NEUROTRANSMITTERS, NEUROPEPTIDES AND THEIR RECEPTORS

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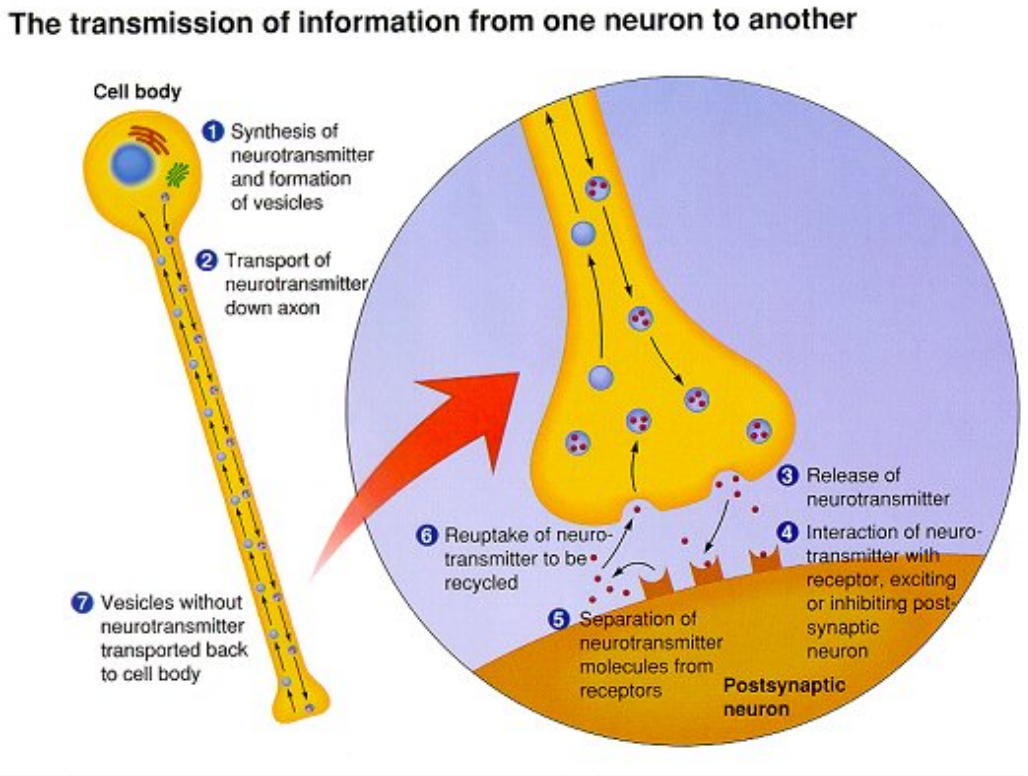
- Literature
- Siegel and Sapru, Essential Neuroscience, chapter 8
- Kandel, Schwartz and Jessel, Principles of Neural Science, chapter 12 (part)

Objectives

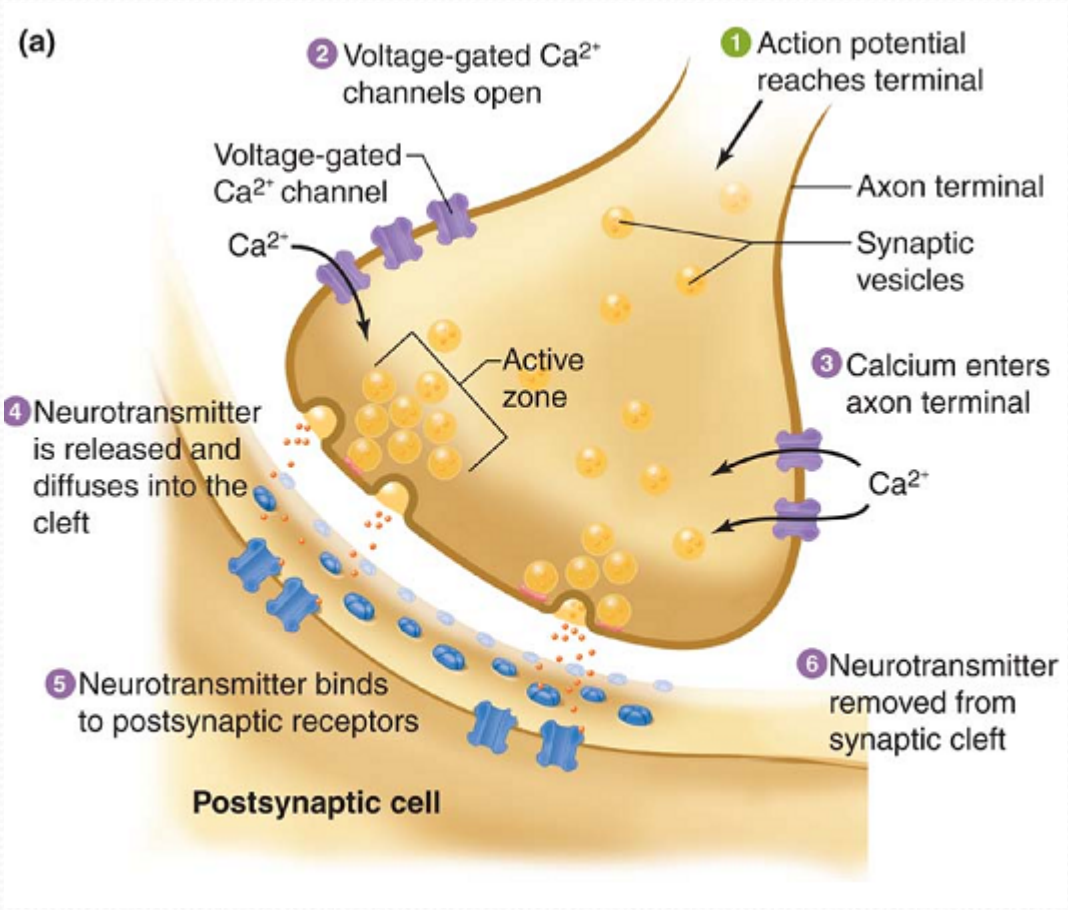
- The definition of a neurotransmitter
- Criteria for accepting a substance as a neurotransmitter
- Major classes of neurotransmitter and differences between them
- Individual neurotransmitters: receptors and role, synthesis and removal
- Clinical conditions related to transmitter dysfunction

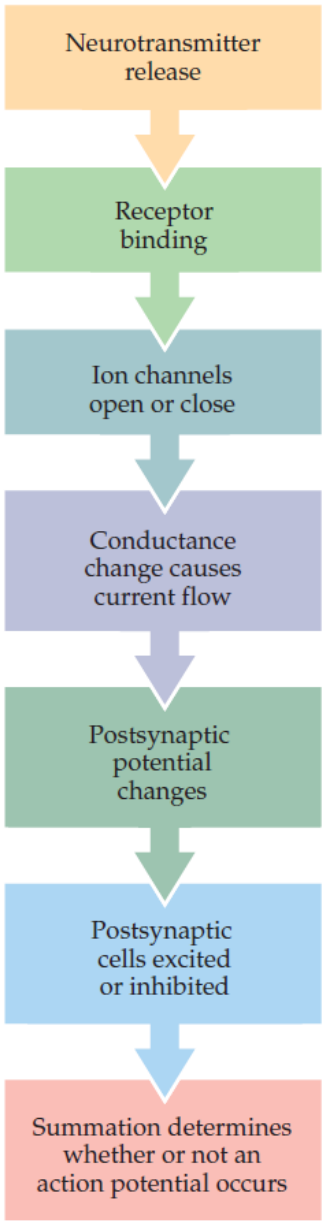
BASICS OF CHEMICAL SIGNALIZATION

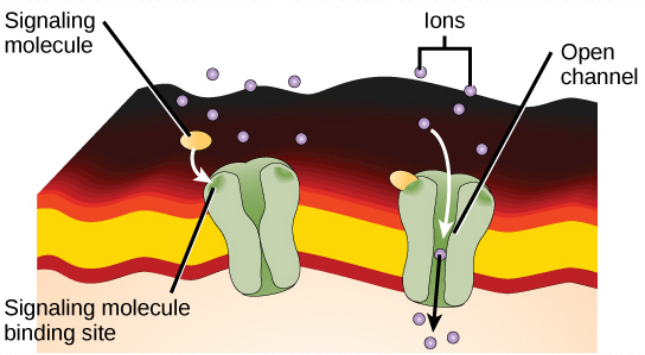
1. Synthesis of the neurotransmitter
2. Transport and storage of the neurotransmitter into the vesicles
3. Release of neurotransmitter
4. Binding of the neurotransmitter for the receptors
5. Inactivation of the neurotransmitter

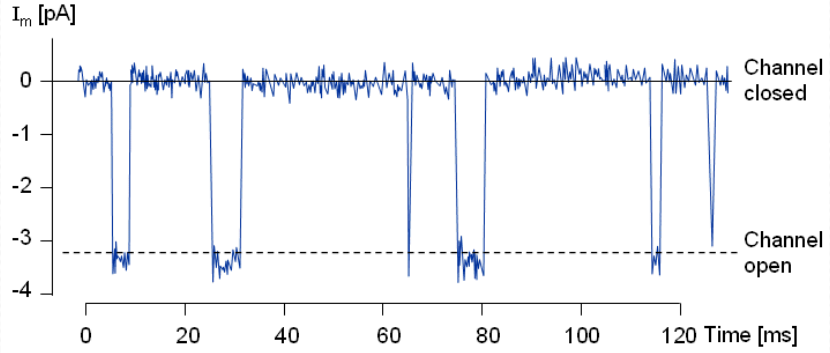


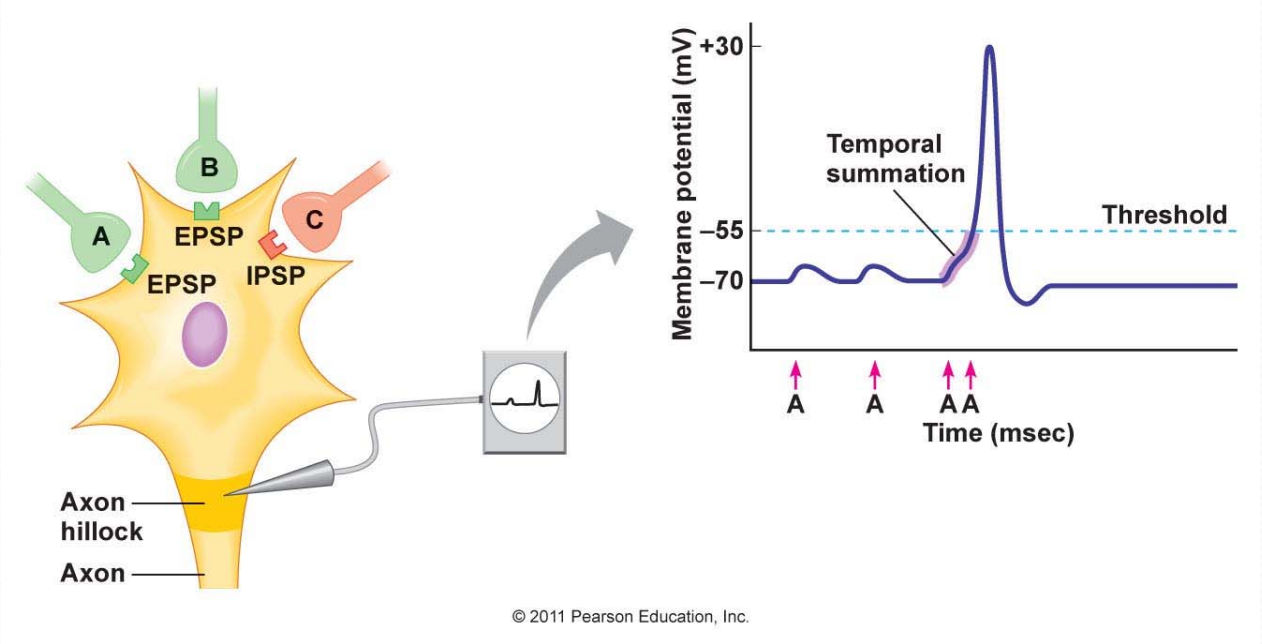
Events from neurotransmitter release to postsynaptic excitation or inhibition






Signaling molecule
Ions
Open channel
Signaling molecule binding site


I_m [pA]
0
-1
-2
-3
-4
Channel closed
Channel open
0
20
40
60
80
100
120 Time [ms]


A
B
C
EPSP
EPSP
IPSP
Axon hillock
Axon
Membrane potential (mV)
+30
–55
–70
Temporal summation
Threshold
A
A
A A
Time (msec)
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- **Neurotransmitter**:
  - Molecule responsible for intercellular signalization
  - Synthesized into the presinaptic neuron
  - Released at a synapse (exocytosis)
  - Binds to the receptors on the postsynaptic cell
  - Elicits a specific response
- Neurotransmitters are electrically charged molecules.
- They are synthesized from the precursor, using the enzymes present in the cytosol.
- The presence of the main enzyme in the neuron can prove its neurotransmitter!

CRITERIA USED FOR IDENTIFYING NEUROTRANSMITTERS

A) PRESYNAPTIC NEURON

1. The substance must be ***PRESENT*** in the nerve terminal
2. ***ENZYMES*** needed for its synthesis must be present
3. It must be released by ***EGZOCYTOSIS*** following depolarization

B) POSTSYNAPTIC MEMBRANE

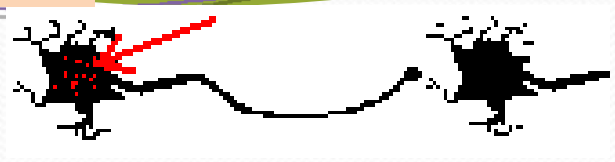
4) It should ***MIMIC*** the action of the endogenously released neurotransmitmimiter when administered exogenously at or near synapse…
5) and activate same ***INTRACELLULAR SIGNAL PATHWAYS***
6) There is a ***MECHANISM OF INACTIVATION***

C) WHOLE MECHANISM

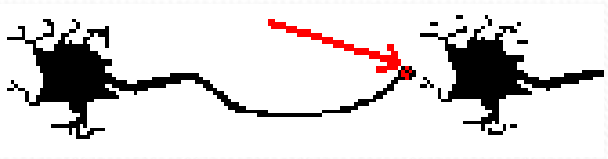
7) ***AGONISTS AND ANTAGONISTS*** evoke the same response

Neurotransmitter Criteria

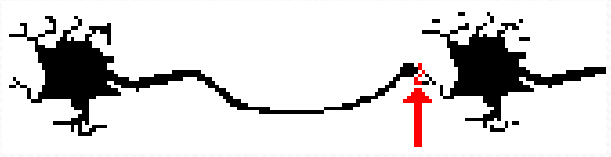
The chemical must be produced within a neuron



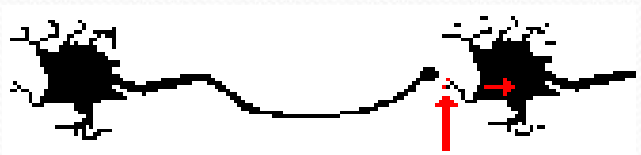
The chemical must be found within a neuron.



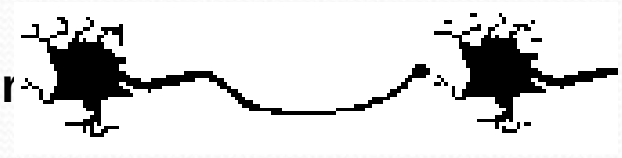
When a neuron is stimulated (depolarized), a neuron must release the chemical.



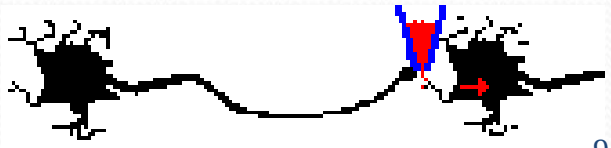
When a chemical is released, it must act on a post-synaptic receptor and cause a biological effect.



After a chemical is released, it must be inactivated. Inactivation can be through a reuptake mechanism or by an enzyme that stops the action of the chemical.



If the chemical is applied on the post-synaptic membrane, it should have the same effect as when it is released by a neuron.



- Besides ***classical neurotransmitters***, neurons can use ***neuroactive peptides*** for sinaptic signalization.

- Neurotransmitsers and neuropeptides have different characteristics and different criteria of identification.

Major Classes of Neurotransmitters

Small-Molecule Neurotransmitters	Neuropeptides	Gaseous Neurotransmitters
Acetylcholine	Opioid peptides	Nitric oxide
Excitatory amino acids	β-endorphin	
Glutamate	Methionine-enkephalin	
Aspartate	Leucine-enkephalin	
Inhibitory amino acids	Endomorphins	
GABA	Nociceptin	
Glycine		
Biogenic amines	Substance P	
Catecholamines		
Dopamine		
Norepinephrine		
Epinephrine		
Indoleamine		
Serotonin (5-HT)		
Imidazole amine		
Histamine		
Purines		
ATP		
Adenosine		

Small Molecule Neurotransmitter Substances

Amines and ACh

- Norepinephrine (NE)
- Serotonin (5-HT)
- Histamine
- Dopamine (DA)
- Epinephrine
- Acetylcholine (ACh)

Amino Acids

- Gamma-aminobutyric acid (GABA)
- Glycine
- Glutamate
- Aspartate

Characteristics of classical neurotransmitters and neuropeptides

- **Neurotransmitters**
- Medium to high concentration
- Lower affinity binding for receptors
- Small potency
- High specificity
- Medium speed synthesis
- Small molecules (2-10 C atoms)
- Mediators (excitatory or inhibitory)

- **Neuropeptides**
- Very low concentration
- High affinity binding for receptors
- high potency
- High specificity
- Slow synthesis (in vitro)
- Small to big molecules (2-100 C atoms)
- modulators

Selected Bioactive Peptides

Hypothalamic releasing factors

CRH: corticotropin releasing hormone
GHRH: growth hormone releasing hormone
GnRH: gonadotropin releasing hormone
Somatostatin
TRH: thyrotropin releasing hormone

Pituitary hormones

ACTH: adrenocorticotropic hormone
αMSH: α-melanocyte stimulating hormone
β-endorphin
GH: growth hormone
PRL: prolactin
FSH: follicle stimulating hormone
LH: luteinizing hormone
TSH: thyrotropin [thyroid stimulating hormone]

GI and brain peptides

CCK: cholecystokinin
Gastrin
GRP: gastrin releasing peptide
Motilin
Neurotensin
Substance K; substance P (tachykinins)

Circulating

Angiotensin
Bradykinin

Frog skin

Bombesin
Caerulein
Ranatensin

Opiate peptides

β-endorphin
Dynorphin
Leu-enkephalin
Met-enkephalin

Neurohypophyseal peptides

Oxytocin
Vasopressin

Neuronal and endocrine

ANF: atrial natriuretic peptide
CGRP: calcitonin gene-related peptide
VIP: vasoactive intestinal peptide

GI and pancreas

Glucagon
PP: pancreatic polypeptide

Neurons only?

Galanin
Neuromedin K
NPY: neuropeptide Y
PYY: peptide YY

Endocrine only?

Calcitonin
Insulin
Secretin
Parathyroid hormone

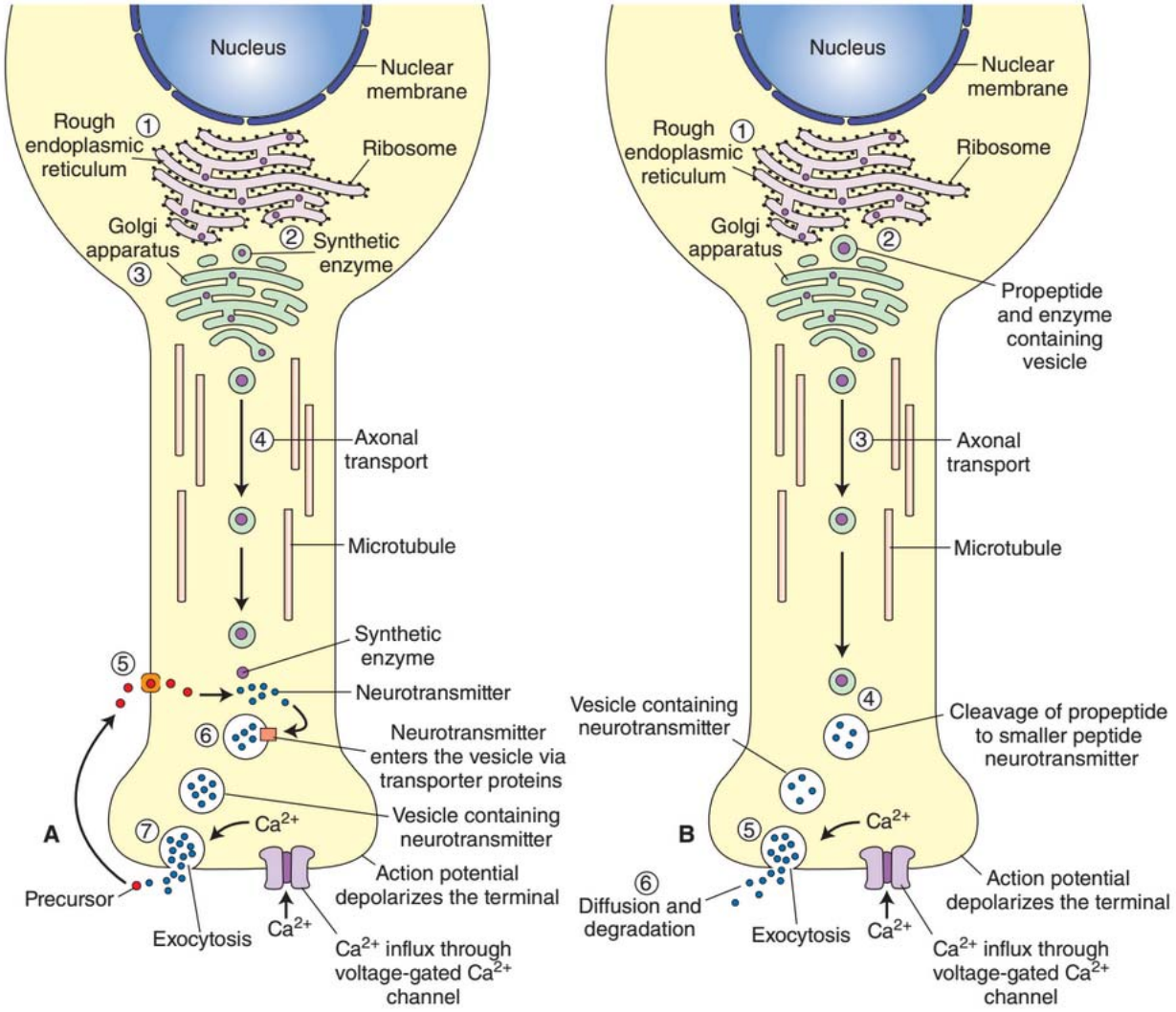


FIGURE 7.4 Steps involved in the synthesis, transport, and release of neurotransmitters. **(A)** Small molecule neurotransmitters. **(B)** Neuropeptides. Ca^{2+}, calcium.

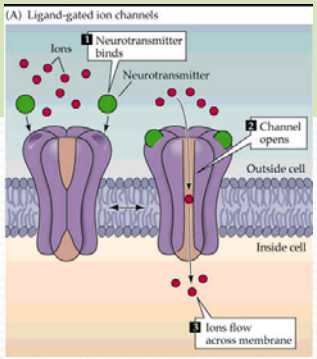
Receptors

- Signalization (either mediated via neurotransmitters or neuropeptides) in chemical synapse depends on RECEPTORS located in the postsynaptic membrane.

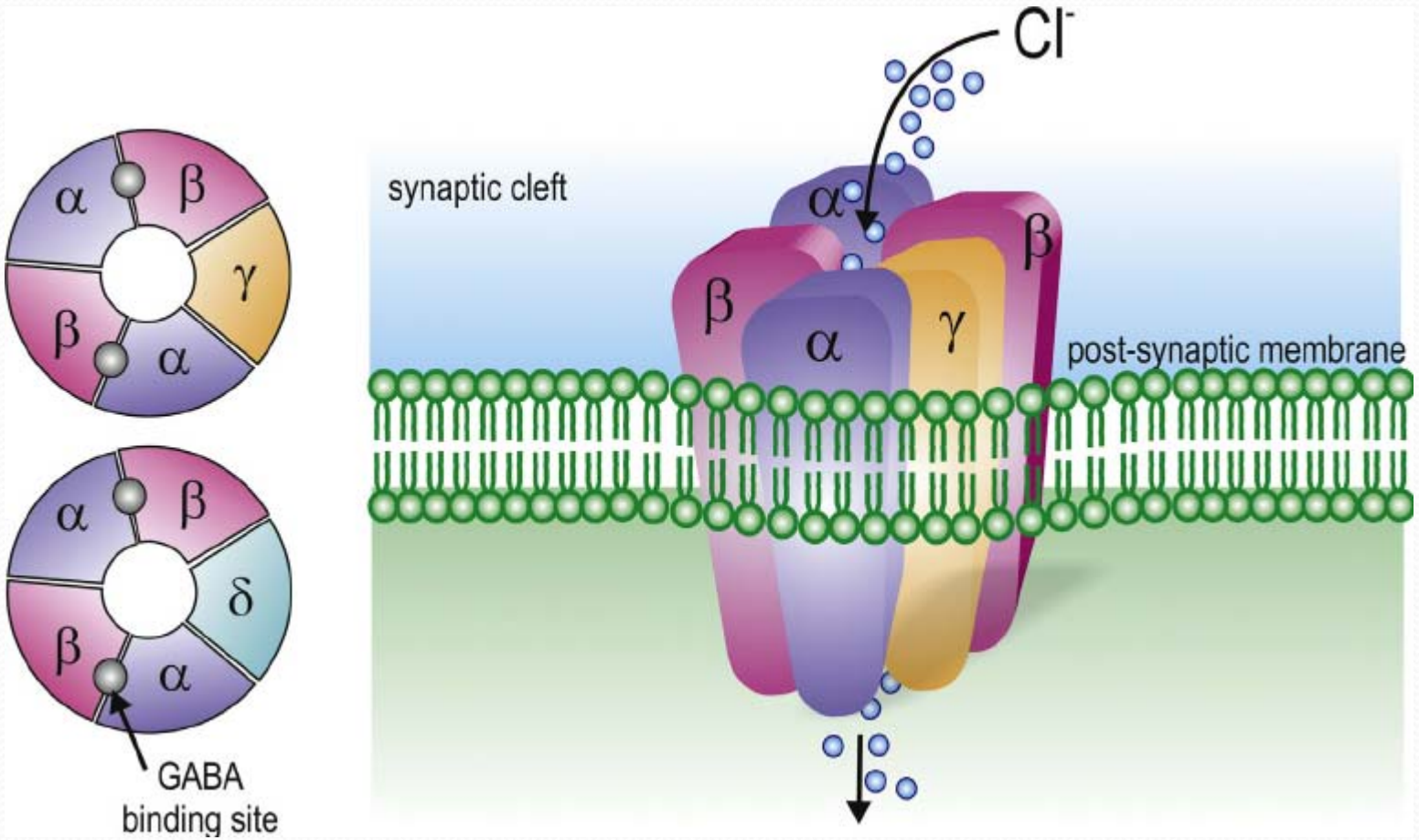
- Receptors can be IONOTROPIC (ligand-gated receptors) or METABOTROPIC (G-protein coupled receptors).

- ***Agonist***- mimics the function of endogenous ligand.
- ***Antagonist*** – binds for receptor and stops the function of the endogenous ligand. They are inhibitors or blockators. They can be competitive or non-competitive.

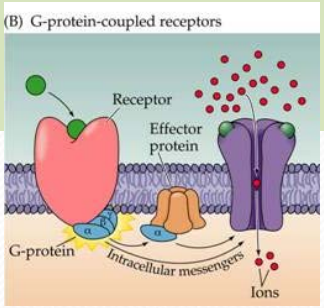
Receptors determine the type and duration of the synaptic signalization



- **Ionotropic**
  - Ligand-gated ion channels (receptors)
  - Combine transmitter binding and channel function into one molecular entity.
  - Rapid (0.1 – 2 ms) and short-duration (≈20 ms) responses
  - Mediatory role
  - Excitatory (Na^+ and K^+ and sometimes Ca^{2+})
  - Inhibitory (Cl^-)
  - Summation of signals is needed to produce an action potential.
  - No voltage dependency except for glu-NMDA receptors


α
β
γ
β
α
α
β
δ
β
α
GABA
binding site
Cl-
synaptic cleft
α
β
β
α
γ
post-synaptic membrane

Receptors determine the type and duration of the synaptic signalization



- **Metabotropic**
  - Slow signalization (100 ms – few sec; 10 000 x slower than ionotropic)
  - Long duration of responses (several minutes)
  - Modulatory role: presynaptic facilitation or inhibition
  - Effect depends on the concentration of the second messengers
  - Duration depends on the enzymes that inactivate second messengers
  - Second messengers stimulate enzymes (protein kinase A) which then phosphorylate appropriate ion channels.

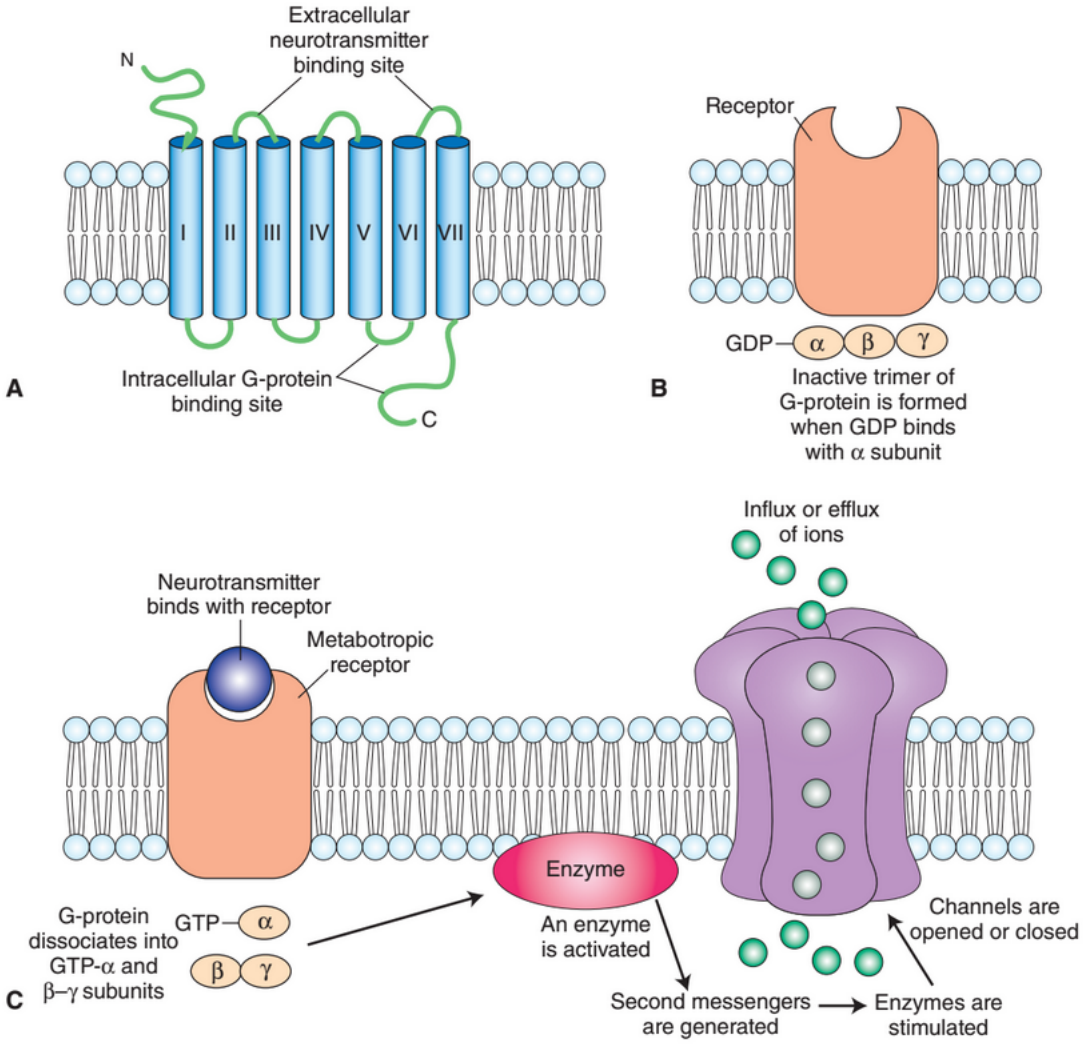


FIGURE 7.20 Metabotropic receptors. **(A)** A single protein (monomeric) molecule with seven membrane-spanning domains (*I–VII*). A neurotransmitter-binding site is located in the extracellular domain (made up of portions of domains II, III, VI, and VII). G-proteins bind to the intracellular loop between domains V and VI and to portions of the C terminus. *N* and *C* denote NH_2 and COOH terminals, respectively. **(B)** Heterotrimeric G-proteins consist of three subunits (alpha, beta, and gamma). When guanosine-5′-diphosphate (GDP) is bound to the α-subunit, the α-subunit binds to β- and γ-subunits, and an inactive trimer is formed. **(C)** The steps of a neurotransmitter binding to the metabotropic receptor and the events that follow. GTP, guanosine triphosphate.

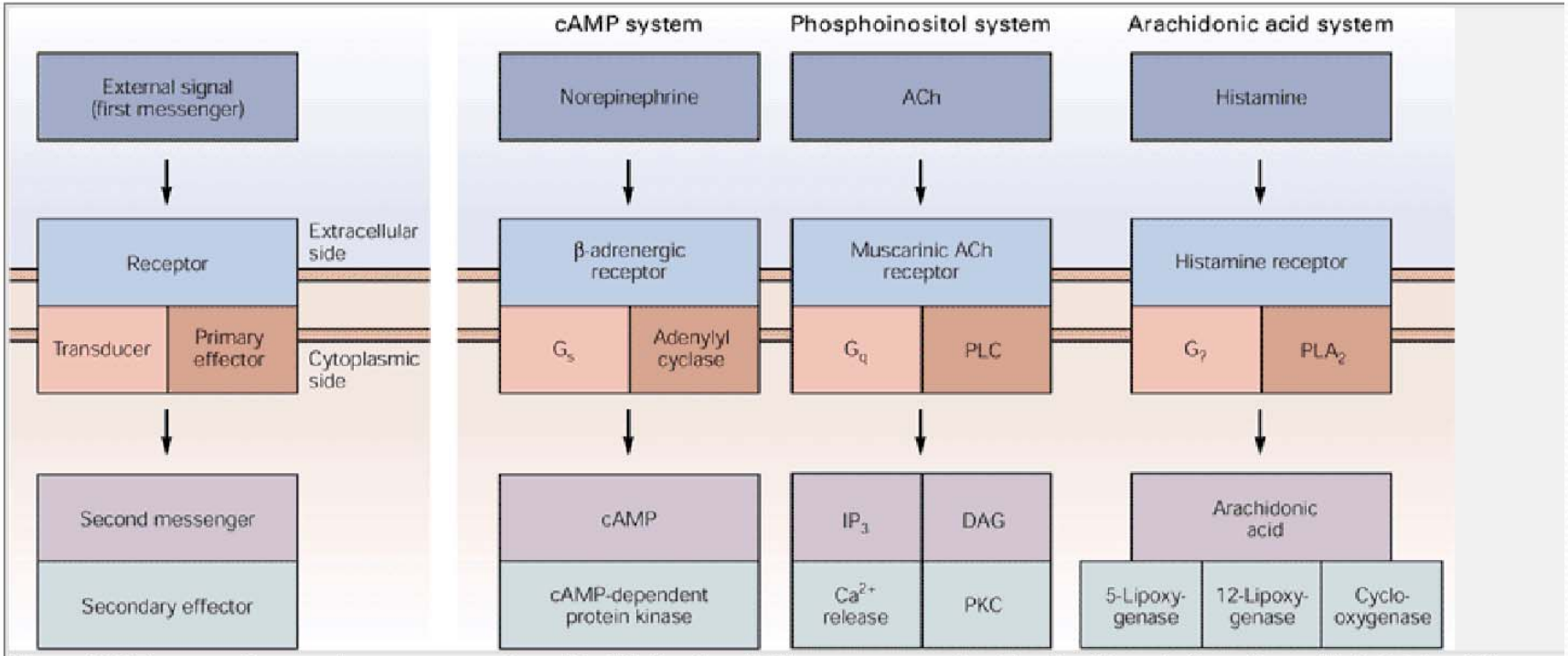


Figure 13-2 The synaptic second-messenger systems identified so far all follow a common plan. The signal-transduction pathways illustrated here follow a common sequence of steps **(left).** Chemical transmitters arriving at receptor molecules in the plasma membrane activate a closely related family of transducer proteins that activate primary effector enzymes. These enzymes produce a second messenger that activates a secondary effector or acts directly on a target (or regulatory) protein.

TABLE 8–3 Ionotropic and Metabotropic Receptors for Different Neurotransmitters

Neurotransmitter	Ionotropic Receptor	Metabotropic Receptor
Acetylcholine (ACh)	Cholinergic nicotinic	Cholinergic muscarinic
Glutamate	NMDA, AMPA, kainate	$mGlu_1$–$mGlu_8$
GABA	$GABA_A$	$GABA_B$
Glycine	Strychnine-sensitive glycine receptor	—
Dopamine	—	D_1-D_5
Norepinephrine	—	α- and β-adrenergic receptors
Epinephrine	—	α- and β-adrenergic receptors
Serotonin	5-HT_3	$5HT_1$, $5HT_2$, $5HT_4$
Histamine	—	H_1, H_2, H_3
Adenosine	—	A_1–A_3
Opioid peptides	—	Mu, delta, kappa, ORL_1

AMPA = alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionate; GABA = gamma aminobutyric acid; NMDA = N-methyl-D-aspartic acid.

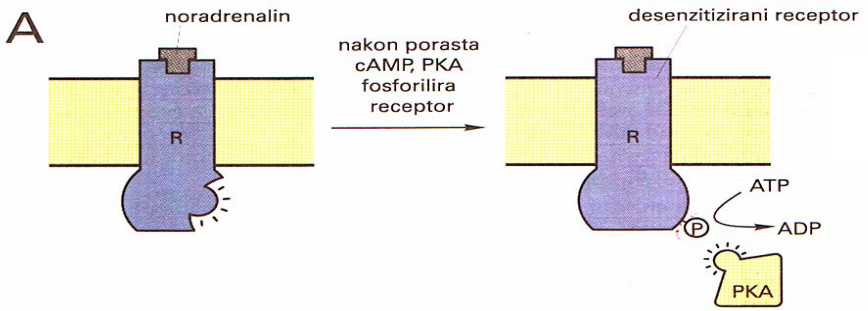
Ionotropic receptors can be excitatory or inhibitory			
Effect	Neurotransmitter	Receptor	Ions
Excitation	Acetylcholine	Nicotinic (nAChR)	Na^+ and K^+
	Glutamate	NMDA	Na^+, K^+ and Ca^+
	Glutamate	Non-NMDA	Na^+ and K^+
	Serotonin	$5\text{-}HT_3$	Na^+ and K^+
Inhibition	GABA	$GABA_A$	Cl^-
	Glycine	Glycine Receptors	Cl^-

Mechanisms of Regulation of Receptors

- Desensitization
- Down-Regulation

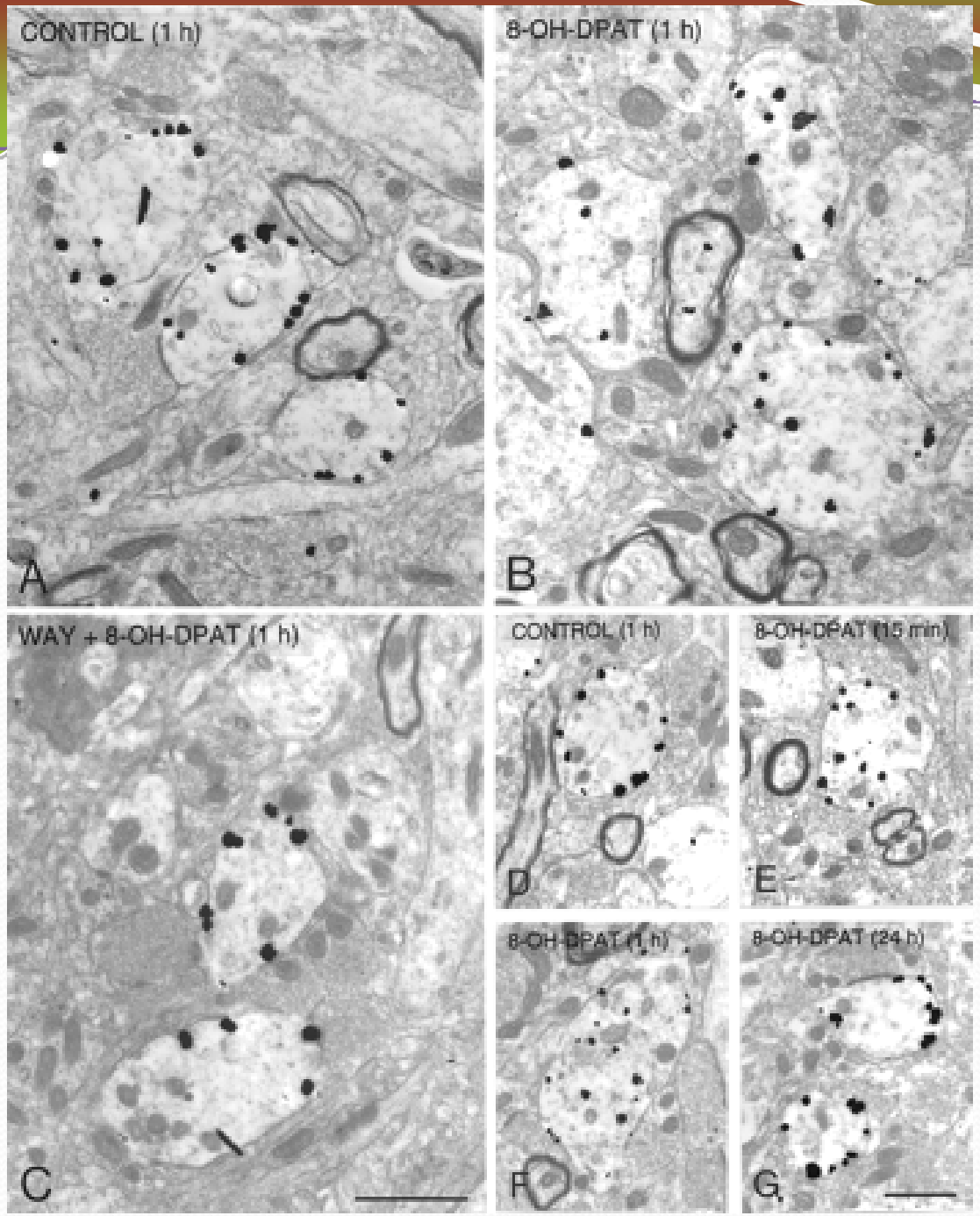
Desensitization

- Prolonged exposure of a receptor to endogenous or exogenous agonist reduces the responsiviness of the receptor.
- NE + β adrenorecptor ⟶ G-protein is stimulated
- cAMP is formed ⟶ protein kinaze A is stimulated
- PKA phosphorylates β adrenorecptor, and uncouples it from the G-protein
- The receptor no longer responds to the agonist = **desensitization**



Down-Regulation

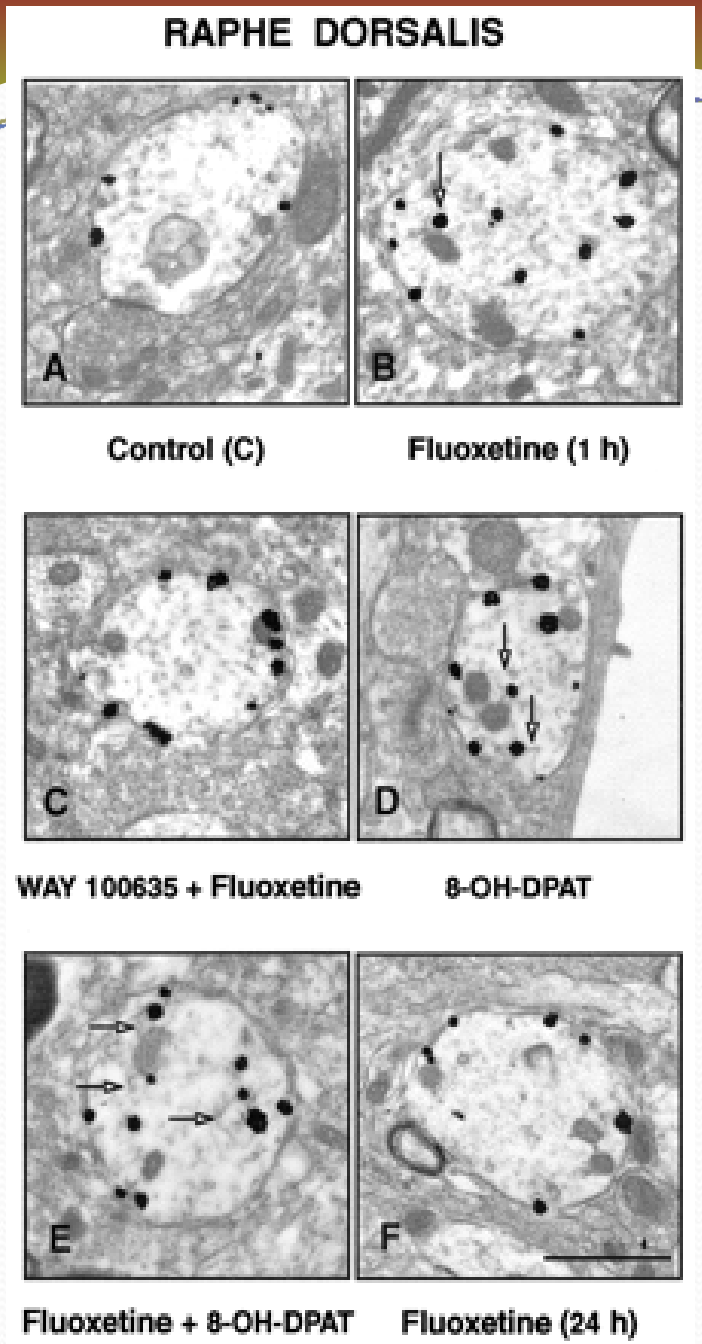
- When the number of receptors decreases.
- Receptors are internalized and sequestered inside the cell.
- Example: 5-HT receptors



INTERNALIZATION OF 5-HT rec

(8-OH-DPAT)

Immunogold labeling of 5-HT_{1A} receptors in dendrites from the NRD
- Riad et al:Internalization of 5-HT_{1A} receptors



INTERNALIZATION OF 5-HT rec

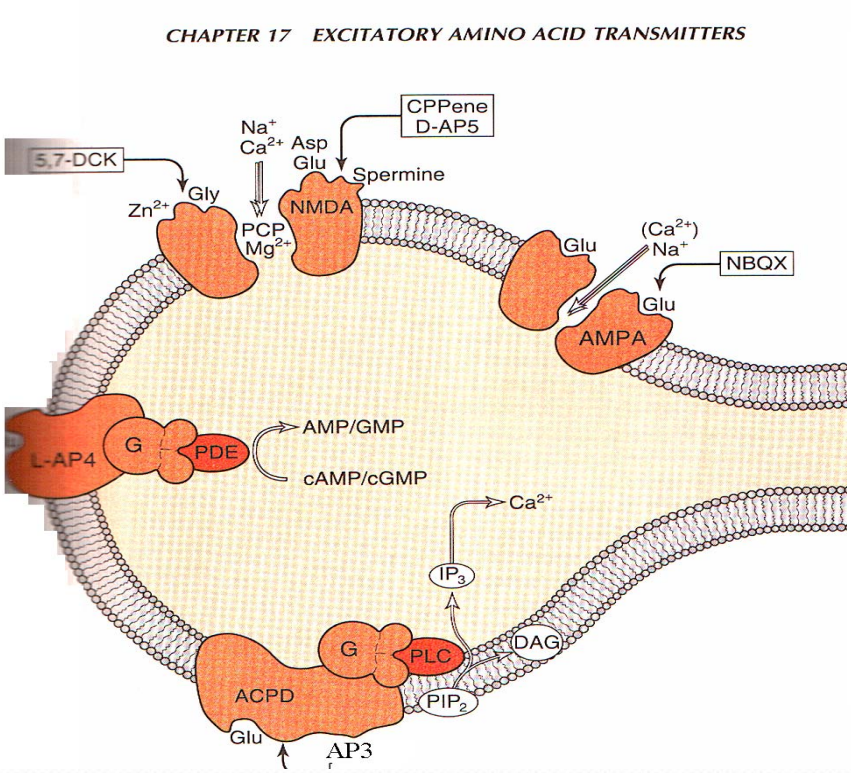
(fluoxetine)

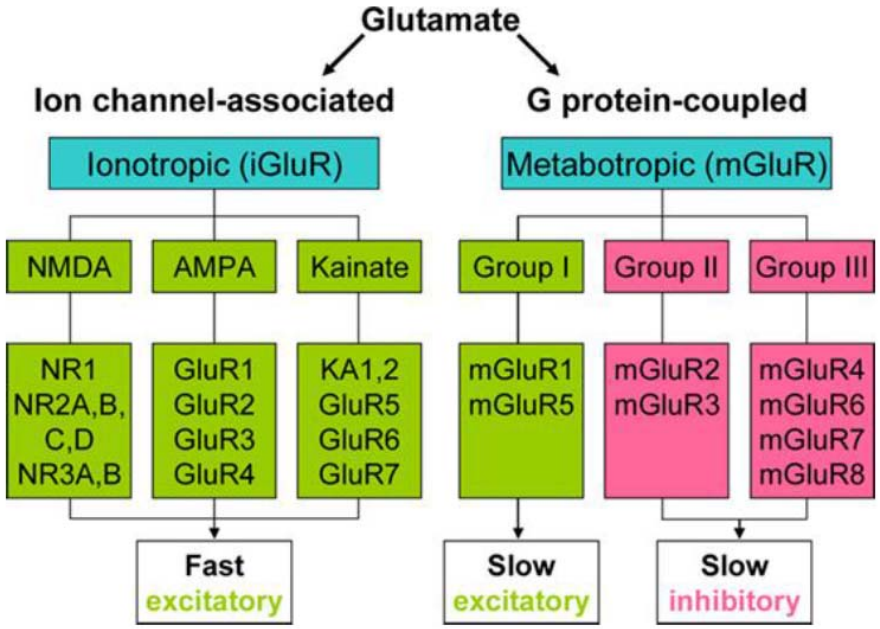
-Immunogold labeling of 5-HT_{1A} receptors in dendrites from the NRD- Riad et al: Internalization of 5-HT_{1A} receptors

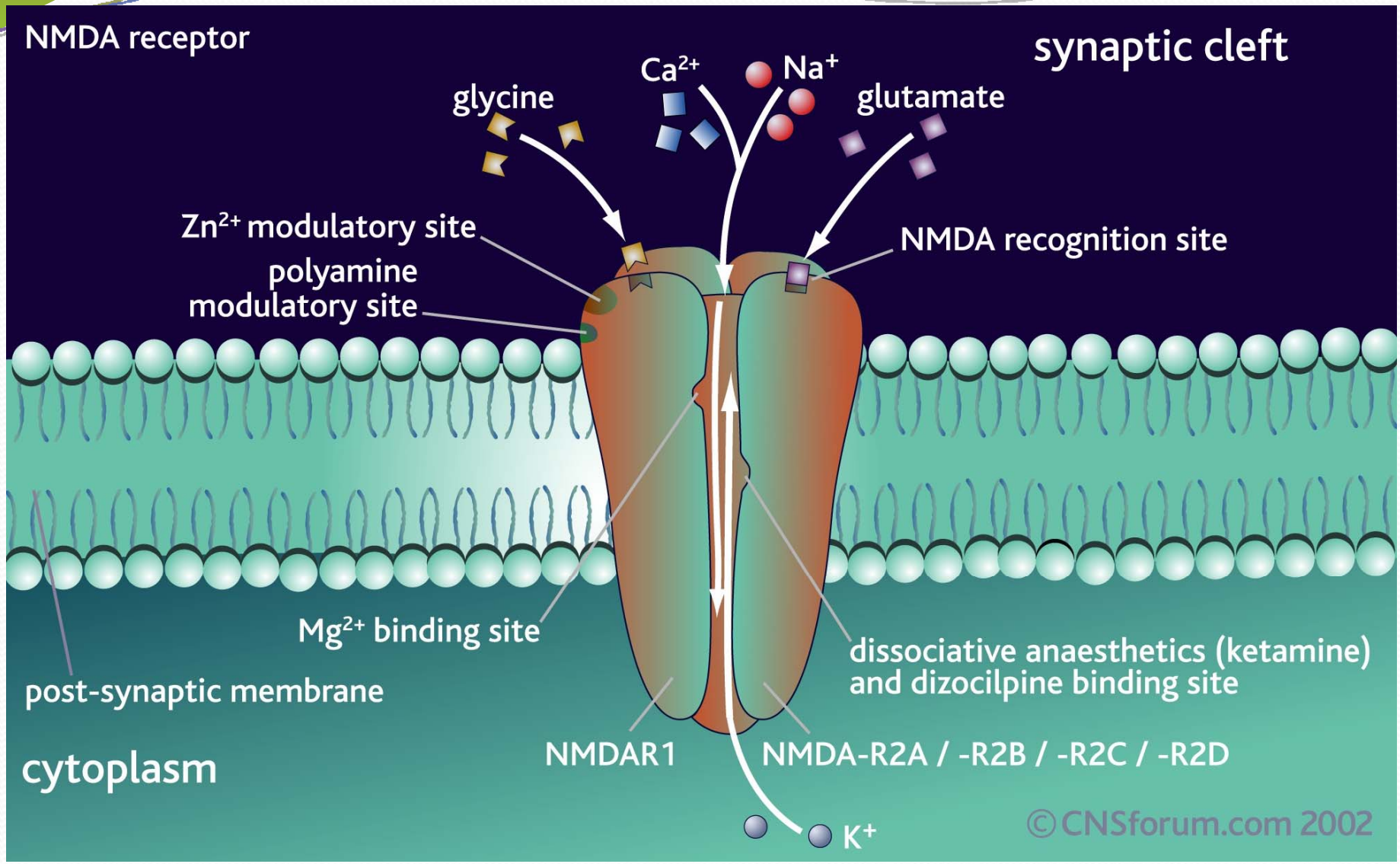
Glutamate

- Excitatory Amino Acid
- neurotransmitter of **fast synaptic excitation**
- Works through ionotropic and metabotropic receptors
- IONOTROPIC glutamate receptors: NMDA, AMPA/kainate
- NMDA receptors: Na^+ gets into the cell to depolarize the membrane – fast synaptic transmission – EPSP
- Ca^{2+} - second messenger: turns electrical signals into biochemical signals – long lasting synaptic effect
- NMDA-receptor is VOLTAGE (partial depolarization) and LIGAND (glutamate) regulated ion channel.

Glutamate receptors

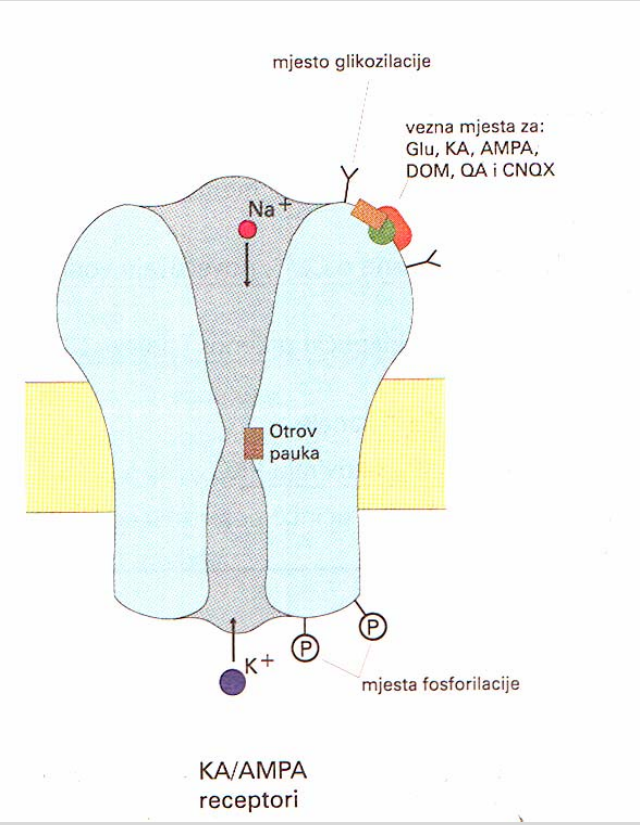





NMDA receptor
synaptic cleft
glycine
Ca2+
Na+
glutamate
Zn2+ modulatory site
polyamine modulatory site
NMDA recognition site
Mg2+ binding site
post-synaptic membrane
dissociative anaesthetics (ketamine) and dizocilpine binding site
cytoplasm
NMDAR1
NMDA-R2A / -R2B / -R2C / -R2D
K+
©CNSforum.com 2002

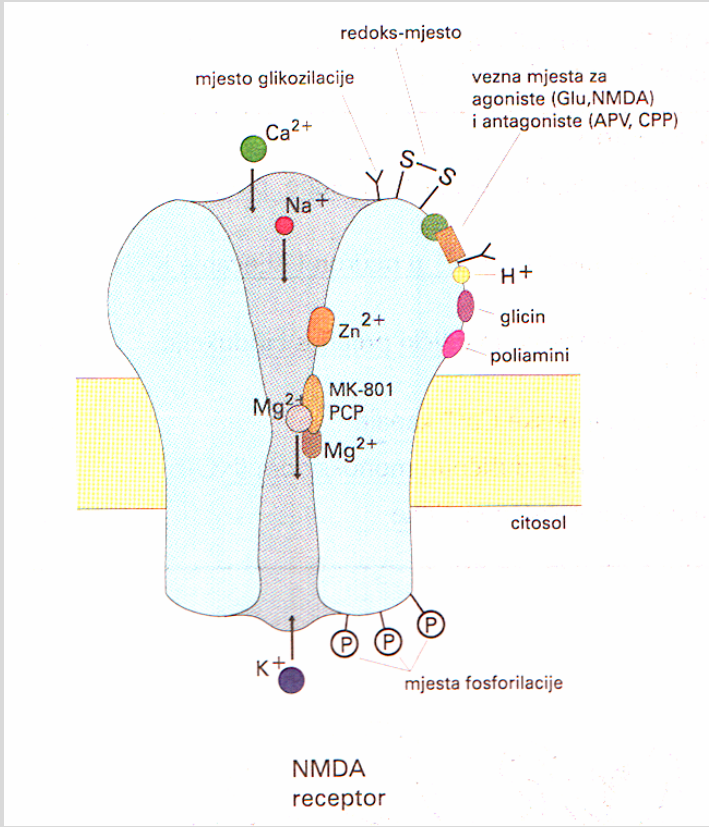
non-NMDA-receptor

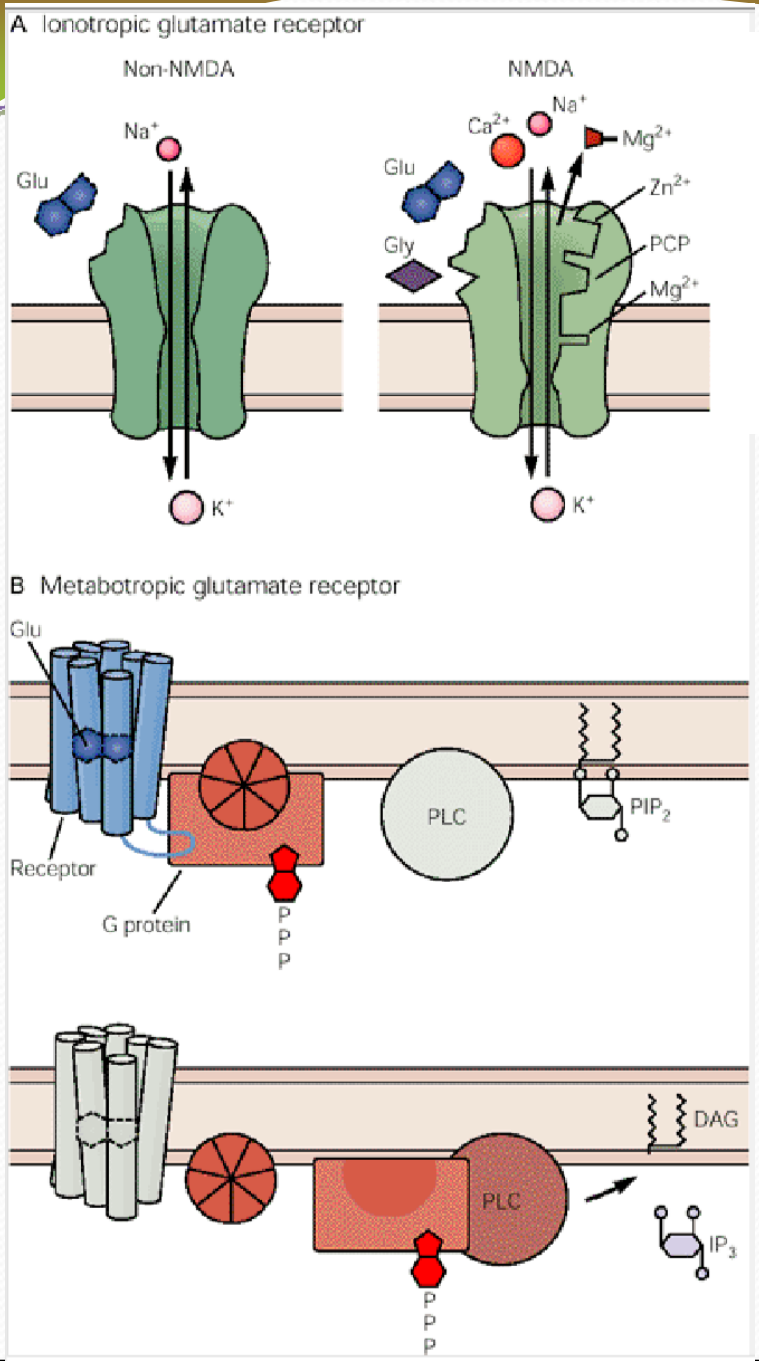
- activated by glutamate
- Na^+ gets into the cell

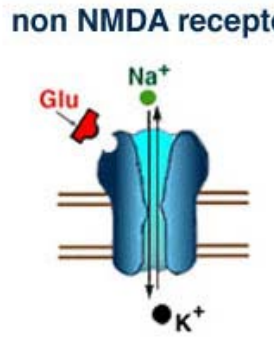


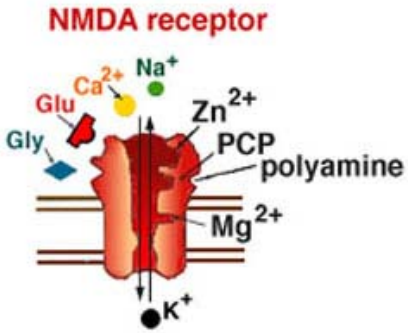
NMDA-receptor

- Activated by potential and glutamate
- Role of Mg^{++}
- Na^+ and Ca^{++} get inside, K^+ goes out
- Ca^{++} -second messenger, important for LTP learning
- glycine









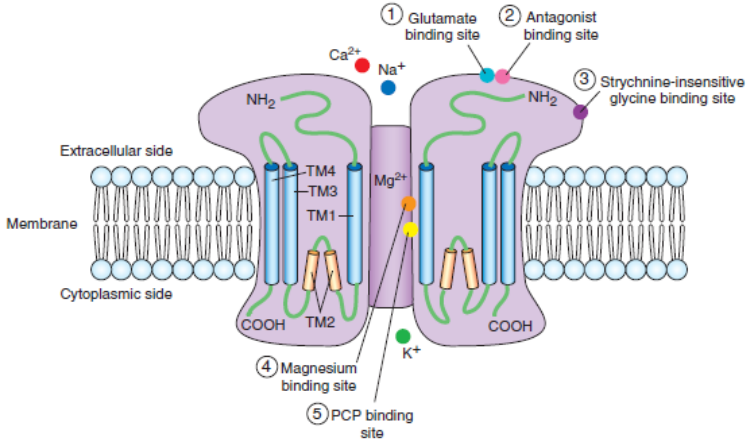


FIGURE 8–18 Components of an N-methyl-D-aspartic acid (NMDA) receptor. PCP = phencyclidine; Ca^{2+} = calcium; Na^{+} = sodium; K^{+} = potassium; Mg^{2+} = magnesium.

- **METABOTROPIC** glutamate receptors
- mGluR1 i mGluR5 activate phospholipase C (PLC) to activate PKC
- others inhibit adenylate cyklase and production of cAMP
- they block excitatory synaptic transmission
- multiple effects and characteristic

- Metabotropic glutamate receptors
  - Increase excitability
  - Block excitatory synaptic transmission and occurence of LTP
  - Block voltage gated Ca^{2+} channels
  - Decrease excitotoxic effects mediated via NMDA receptors

Metabolism of glutamate

Synthesis

- Glutamate is synthesized in the brain by two processes.
- **1. Process**: glucose enters the neuron by facilitated diffusion and is metabolized via the Krebs (tricarboxylic acid) cycle
- α-oxoglutarate generated during the Krebs cycle is transaminated by α-oxoglutarate transaminase to form glutamate.

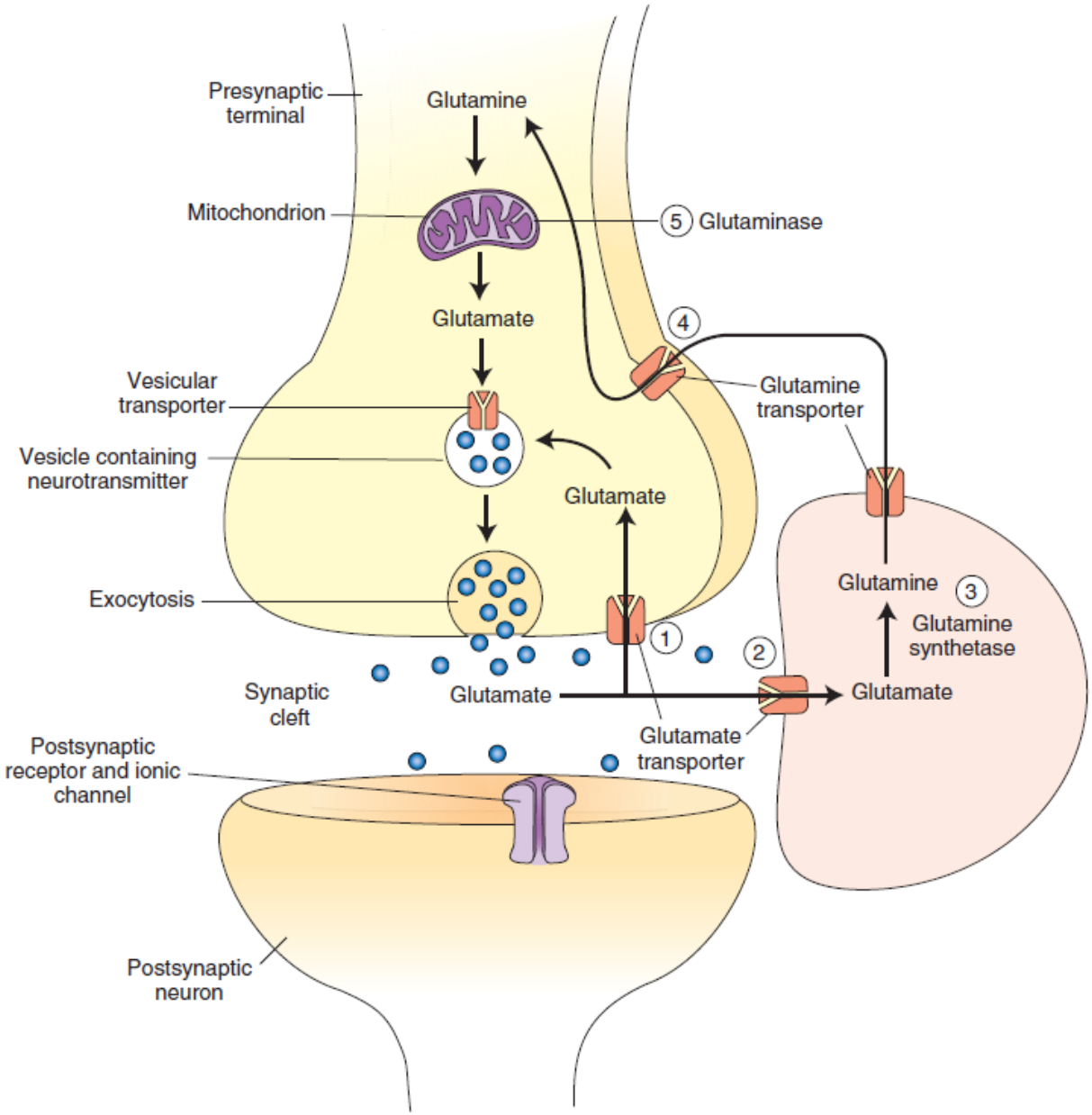


FIGURE 8–7 Steps involved in the synthesis and release of glutamate.

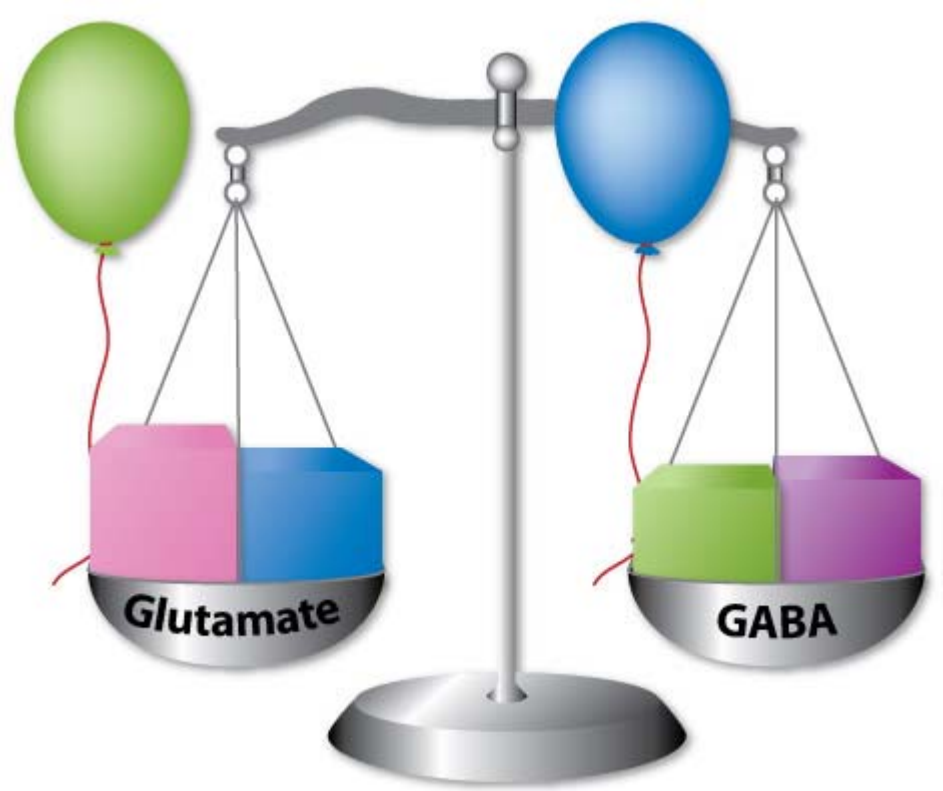
- **2. Process:**
- 1. and 2. Nerve terminals and glial cells reuptake the glutamate released from the nerve terminals via glutamate transporters located in their cell membranes.
- 3. In the glia, glutamate is converted into glutamine by an enzyme, glutamine synthetase.
- 4. Glutamine is transported out of the glia into the neuronal terminal via glutamine transporters located in the glial and neuronal terminal membranes.
- 5. In the neuronal terminal, glutamine is converted into glutamate by an enzyme, glutaminase. Glutamate is taken up into the vesicles by active transport, stored.

Exocytosis

- subsequently released by exocytosis. Released glutamate is then actively taken up by the glia and neuronal terminals via glutamate transporters (GLT-1 and EAAC1).
- In the neuronal terminal, it is repackaged into the vesicles for subsequent reuse. In the glia, it is converted into glutamine.

Physiological and Clinical Considerations

- Learning and memory
- ALS
- Excitotoxycity
- Alzheimer's disease


Glutamate
GABA

GABA and Glycine - main inhibitory amino acid neurotransmitters (fast synaptic inhibition)

- **GABA** – **synthesis and removal**
- 1. Glutamine is converted into glutamate by an enzyme, glutaminase.
- 2. GABA is formed by α-decarboxylation of glutamate. This reaction is catalyzed by a cytosolic enzyme, **L-glutamic acid-1-decarboxylase (GAD)**
- 3. Synthesized GABA is taken up into vesicles where it is stored.
- **4.** It is released into the synaptic cleft by exocytosis.

- 5. After its release, GABA is taken up into presynaptic terminal via GABA transporters and repackaged into vesicles for subsequent use.
- 6. GABA is also taken up into the glia via GABA transporters
- 7. In glia, GABA is converted to **glutamate** by a mitochondrial enzyme, GABA transaminase (GABA-T).
- 8. Another enzyme, glutamine synthetase, converts glutamate into **glutamine**, which is then transported into the neighboring nerve terminals where it is processed to synthesize glutamate.

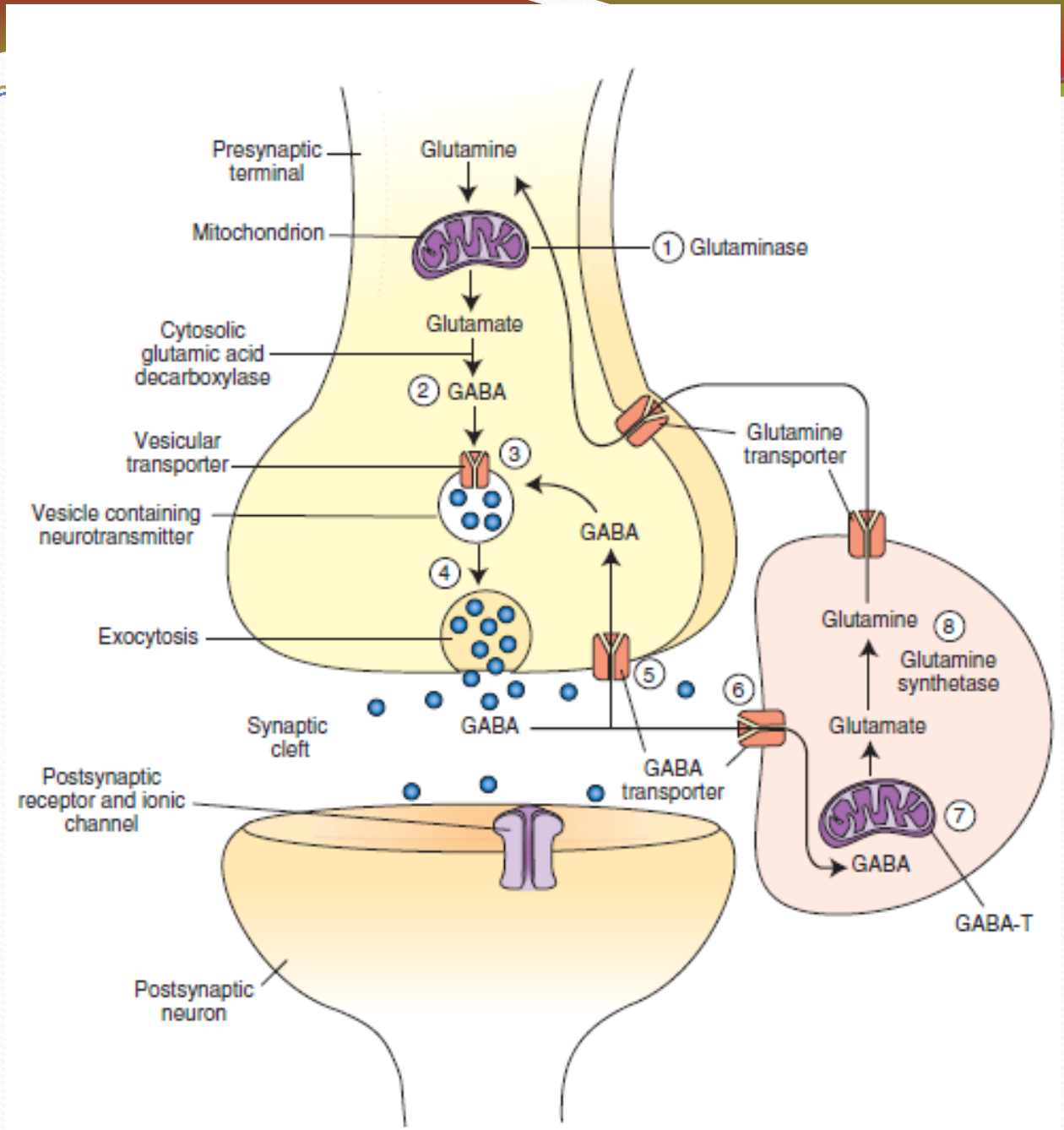


FIGURE 8–8 Steps involved in the synthesis and release of gamma aminobutyric acid (GABA).

Distribution of GABA and Glycine:

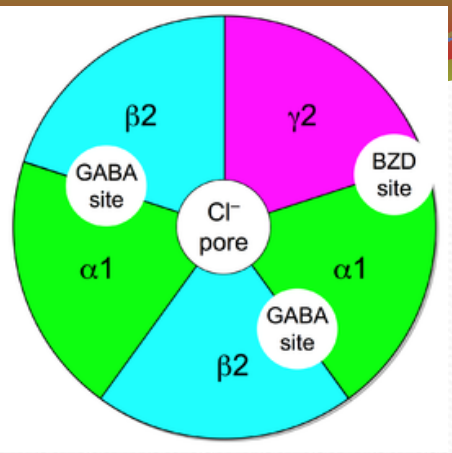
- GABA is found in high concentrations in the brain and spinal cord.
- is absent in peripheral nerves or peripheral tissues

- Glycine is found in the spinal cord, caudal (lower) parts of medulla and retina.

GABA and Glycine

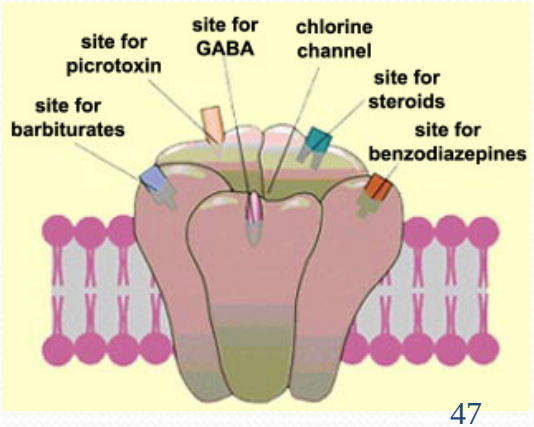
- Bind to ionotropic receptors ($GABA_A$ i Glycine) which are ligand-gated Cl^- channels
- GABA also has a metabotropic receptors ($GABA_B$)
- Glycine works as a coactivator of glutamate NMDA-receptors.

$GABA_A$ receptor



- They consist of five subunits:

  two α, two β, and one γ.
- Each subunit has four trans-membrane domains (TM1–TM4).
- Important binding sites are present on these receptors:
  - benzodiazepines (diazepam [Valium]),
  - barbiturates,
  - steroids,
  - anesthetics,
  - picrotoxin



$GABA_A$ receptor

- Activation of the GABA receptor site by GABA agonists results in the opening of the chloride channel (Cl^-).
- Two molecules of GABA are needed.
- *Inhibitory postsinaptic potential (IPSP)* is formed.

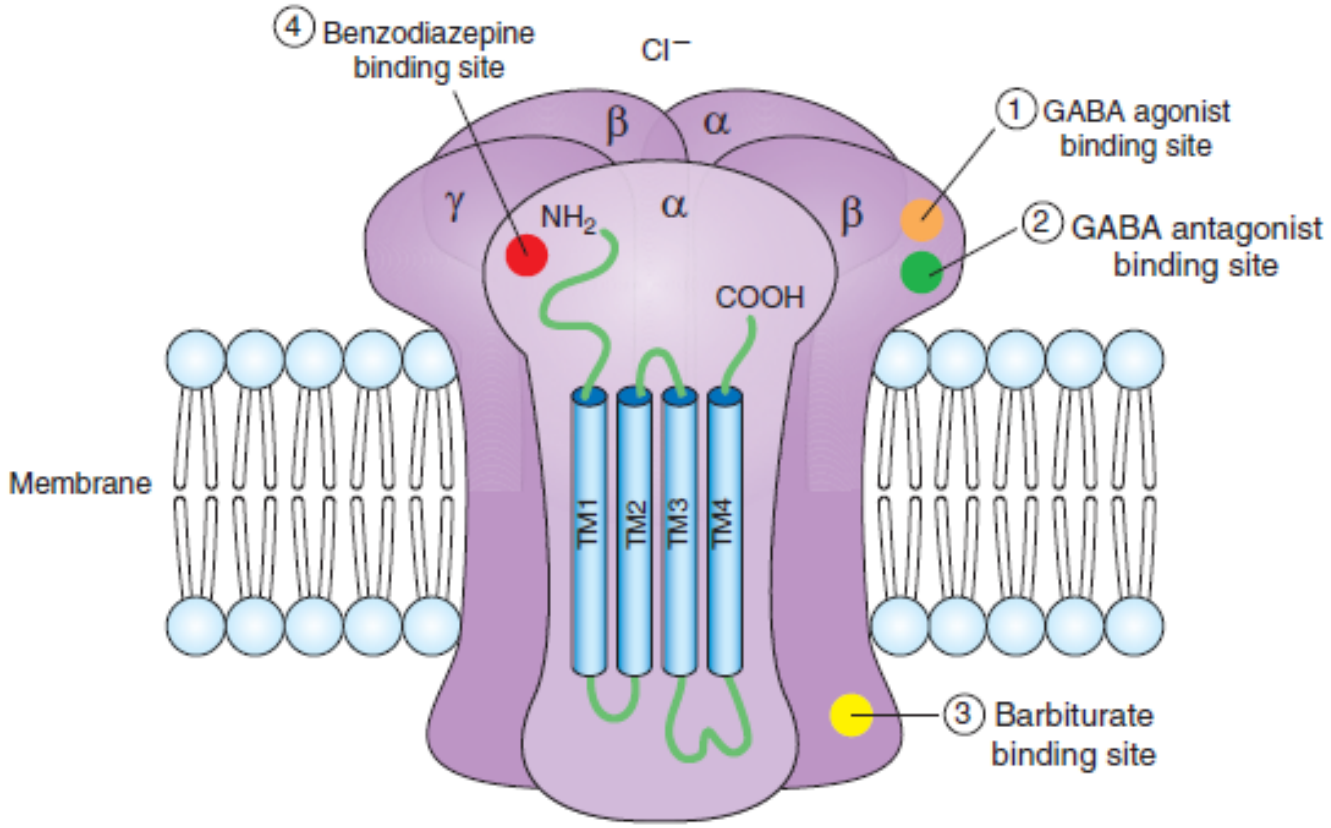


FIGURE 8–19 Components of a gamma aminobutyric acid type A (GABAA) receptor. Cl^- = chloride.

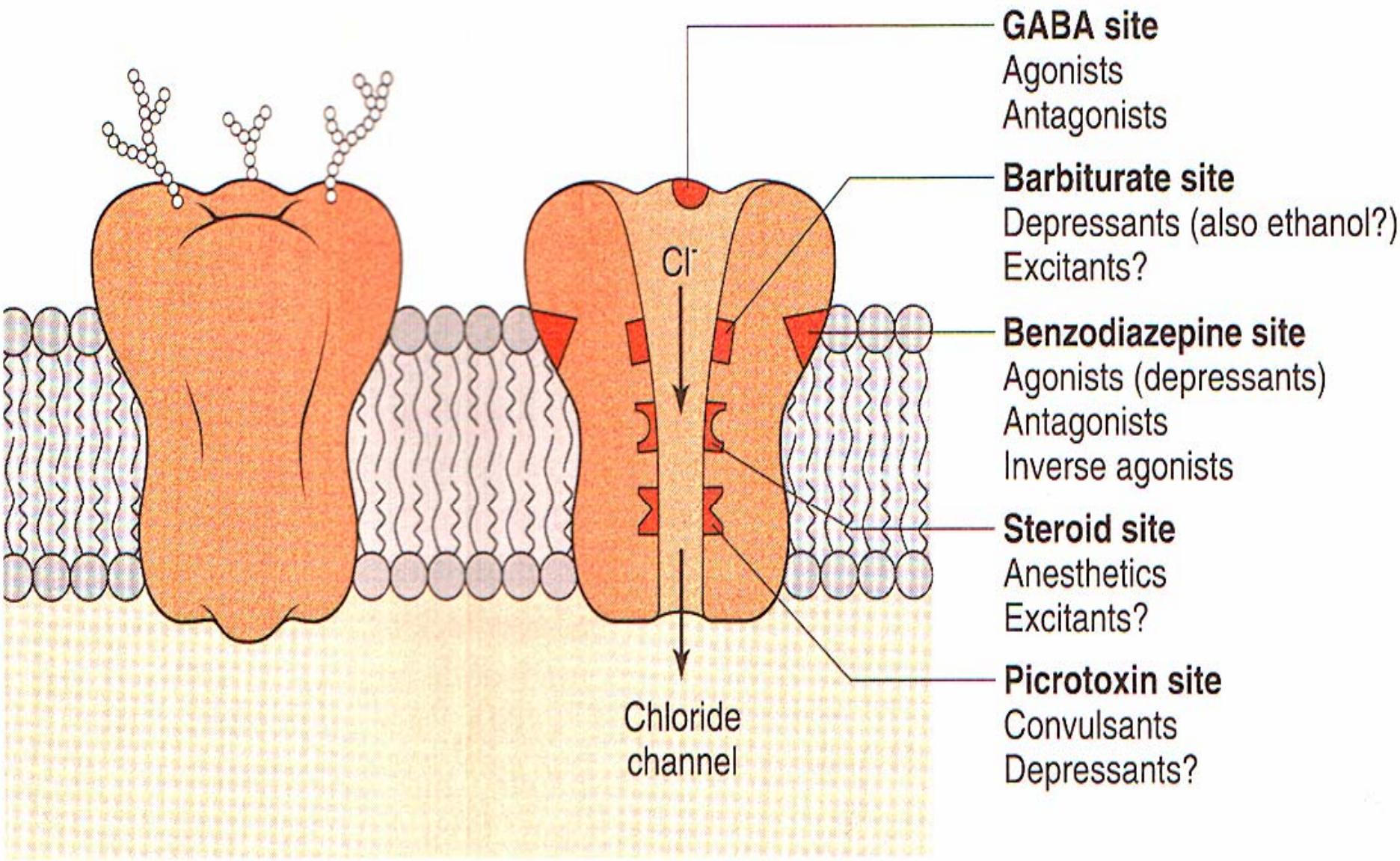
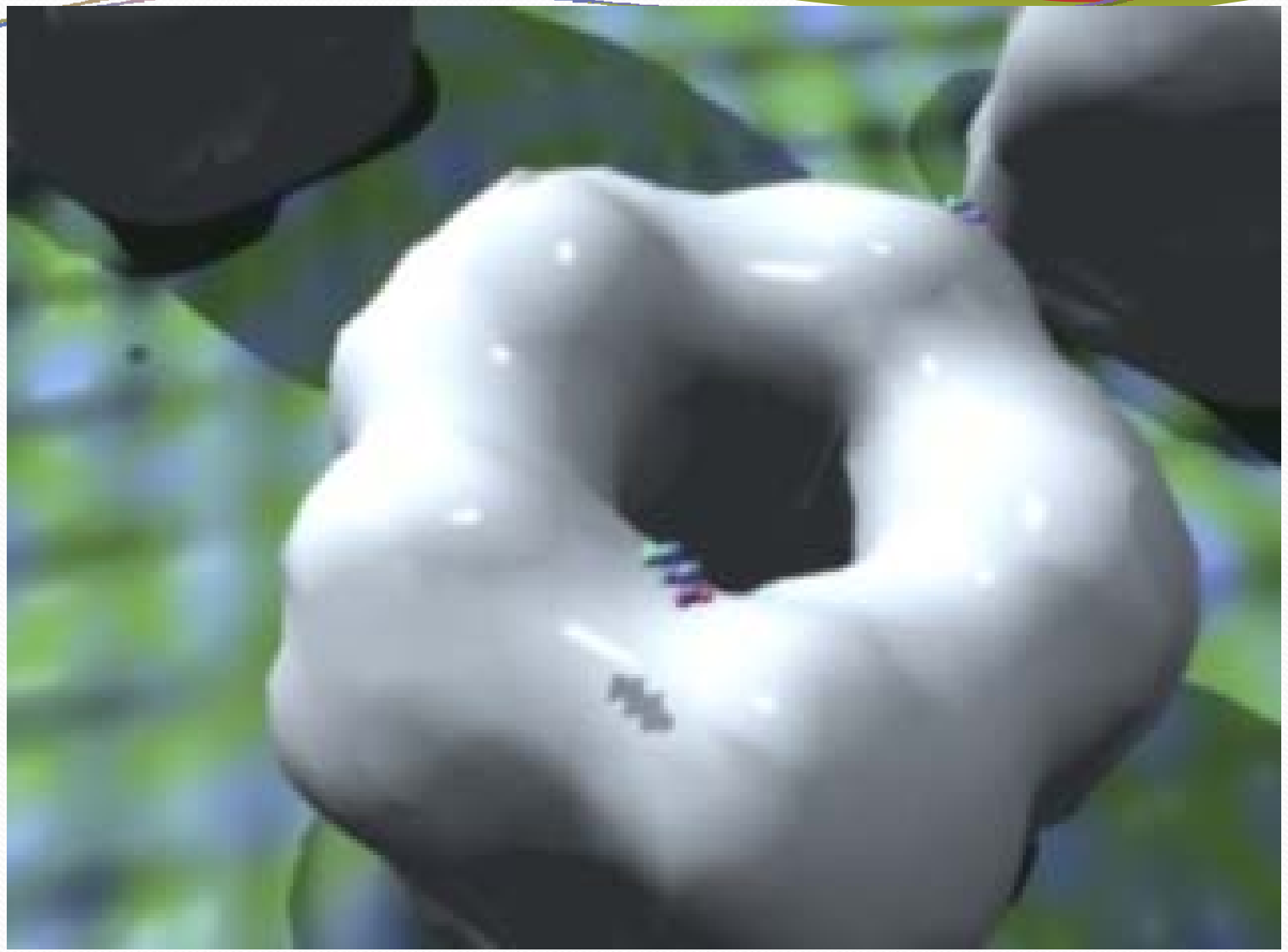
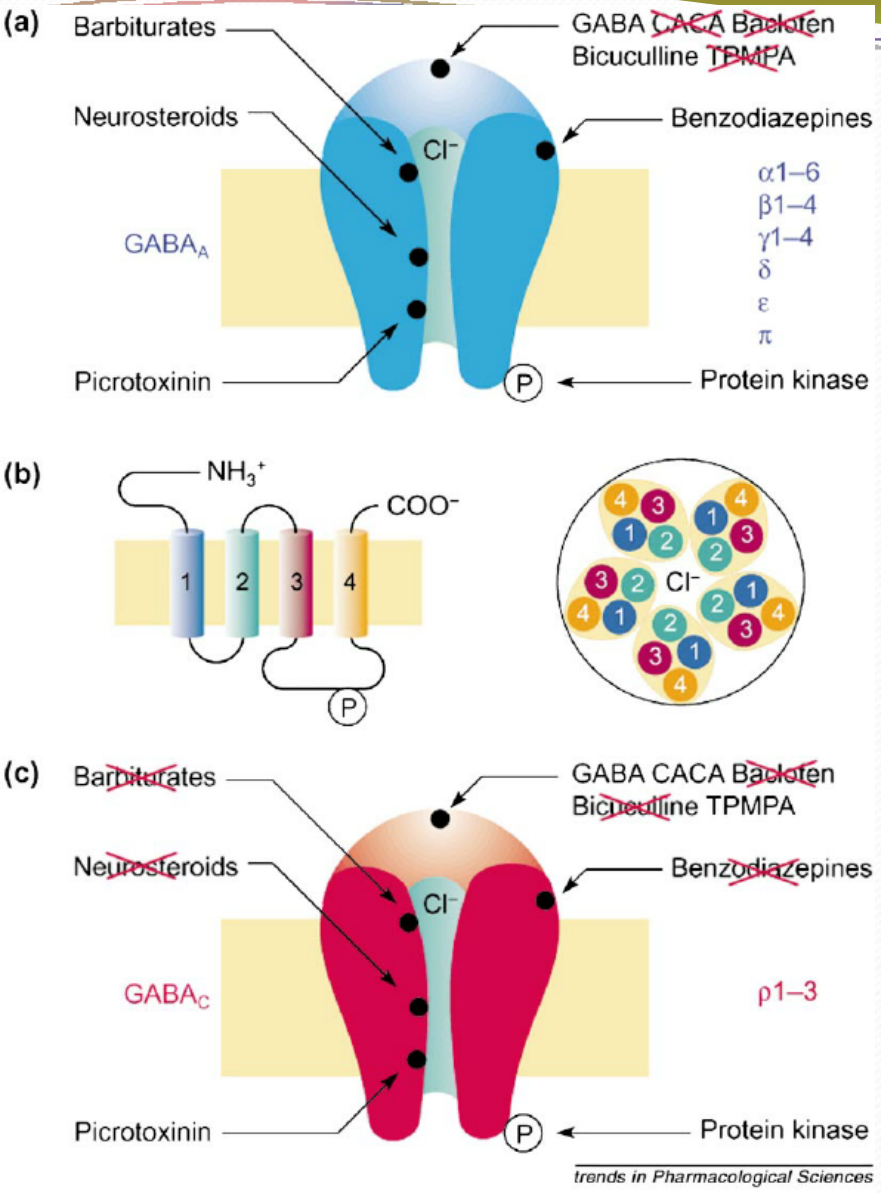


FIG. 2. Structural model of the $GABA_A$/benzodiazepine receptor-chloride (Cl^-) ionophore complex. The *cut-away view* demonstrates targets for a variety of compounds that influence the receptor complex. No specific drug receptor location is implied.



Characteristics of GABA Receptors

	$GABA_A$ Receptor	$GABA_B$ Receptor	$GABA_C$ Receptor
Category	Ligand-gated Channel	G-protein coupled receptor	Ligand-gated Channel
Subunits	a, b, g, d, e, p	GBR1, GBR2	rho
Agonists	Muscimol, THIP	Baclofen	
Antagonists	Bicuculline, Picrotoxin	Phaclofen	TPMPA, Picrotoxin
Desensitization	Yes	No	No
Modulator	Benzodiazepines Barbiturates		Zinc


(a)
Barbiturates
GABA CACA Baclofen
Bicuculline TPMPA
Neurosteroids
Benzodiazepines
Cl⁻
α1–6
β1–4
γ1–4
δ
ε
π
GABA$_A$
Picrotoxinin
P
Protein kinase
(b)
NH$_3^+$
COO⁻
1
2
3
4
P
Cl⁻
(c)
Barbiturates
GABA CACA Baclofen
Bicuculline TPMPA
Neurosteroids
Benzodiazepines
Cl⁻
GABA$_C$
ρ1–3
Picrotoxinin
P
Protein kinase
trends in Pharmacological Sciences

$GABA_A$ receptor ANTAGONISTS

- Selective competitive antagonist BICUCULLINE decreases frequency and duration of opened stage.
- PICROTOXINE – noncompetitive alosteric inhibitor – prevents the opening of the channel.

$GABA_A$ receptor AGONISTS

- MUSCIMOL
- BENZODIAZEPINES – increase the frequency of the open stage (anxiolitics, antiepileptics, hypnotics, muscle relaxans)
- BARBITURATES – stimulate the effect of GABA on receptor, but can open Cl- channel with no GABA present (sedatives, hypnotics, anticonvulzives, anestetics)
- PROGESTERONE– sedative; prolonges duration of the opening stage.

- $GABA_B$ receptor: increases membrane permeability for K^+ (hyperpolarization), and decreases permeability for Ca^{2+} = development of slow IPSP

Glycine

- Glycine hyperpolarizes neurons by opening chloride channels.
- AGONISTS of Glycine receptors:
  - taurin, beta-alanin
- ANTAGONIST:
  - strihnin –source the plant *Strychinos nux vomica;* neurotoxin, evokes convulsions

Physiological and Clinical Cosiderations

- Huntington's chorea, Parkinson's disease, senile dementia, Alzheimer's disease, schizophrenia
- Vit B6 deficiency in infant feeding formula
- Epileptic seizures
- **hyperglycinemia, is** devastating neonatal disease characterized by lethargy and mental retardation.

Acetylcholine

synthesis and release

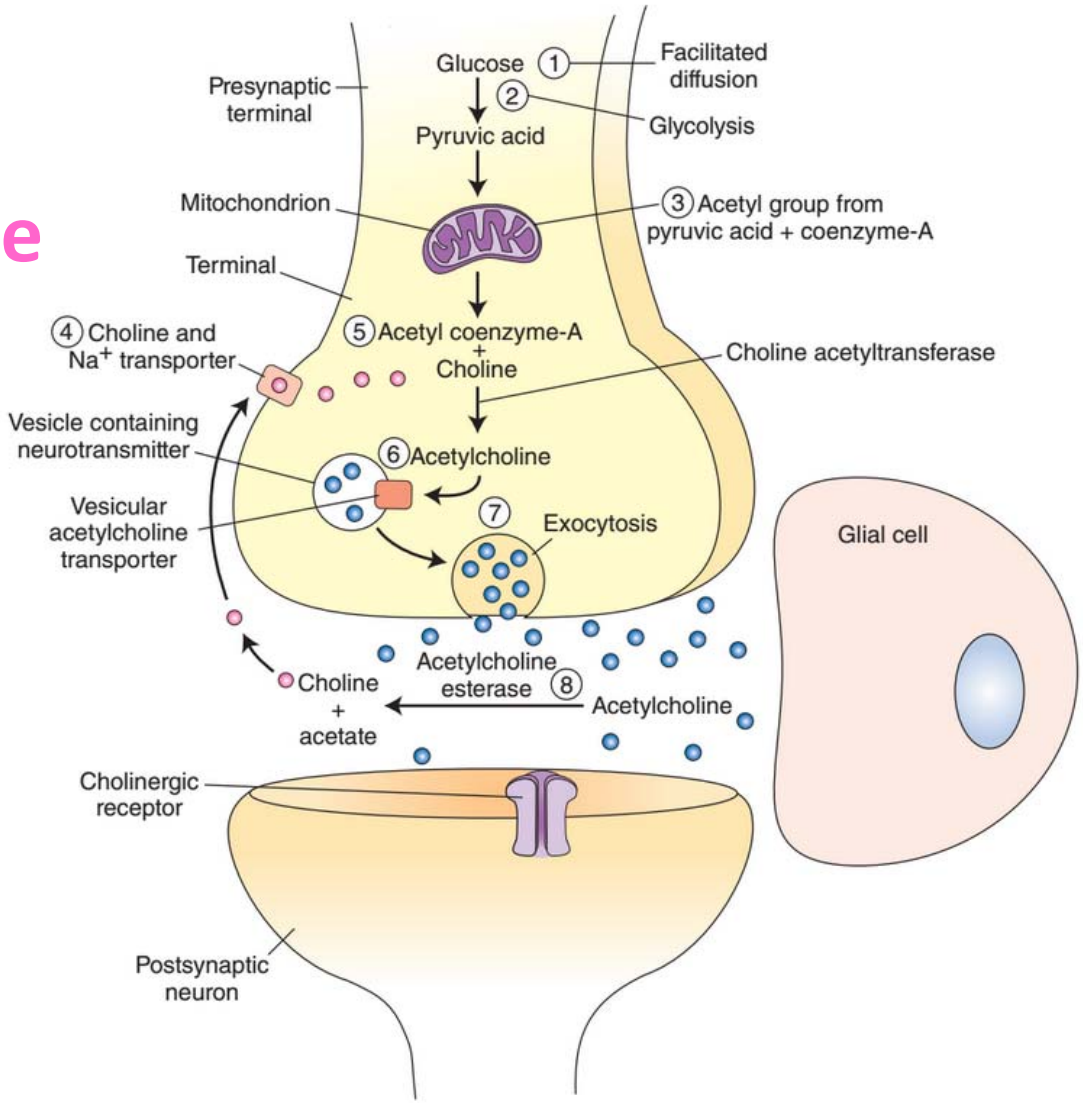
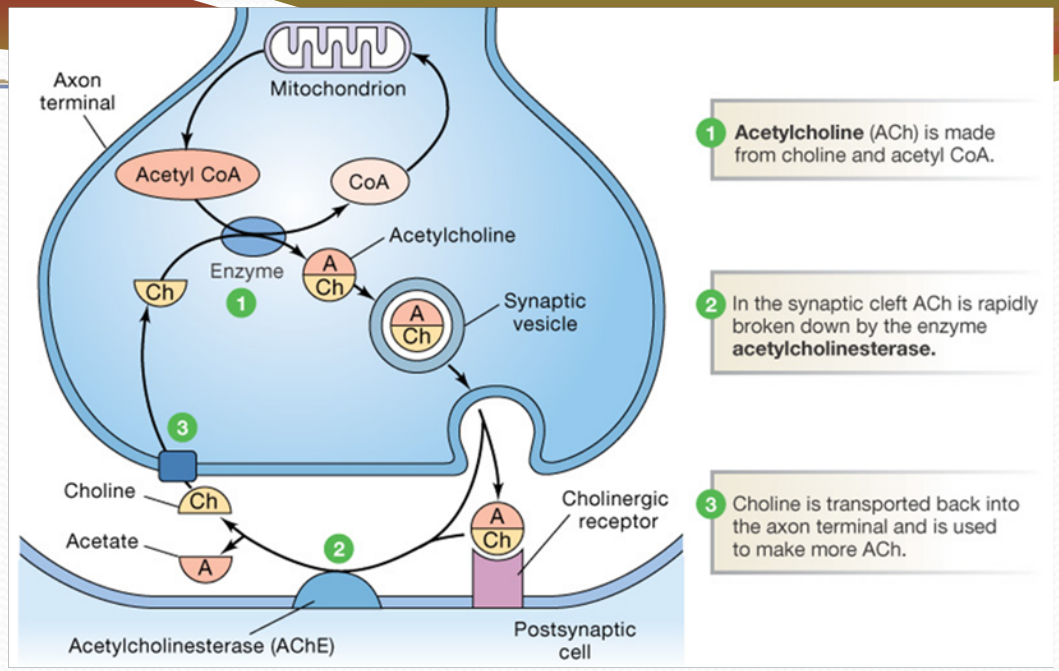


FIGURE 7.5 Steps involved in the synthesis and release of acetylcholine. Na^+, sodium.

- **Synthesis**
- 1. Glucose enters the nerve terminal by passive transport (facilitated diffusion).
- 2. **Glycolysis occurs in the neuronal cytoplasm, and pyruvate** (pyruvic acid) molecules are generated.
- 3. Pyruvate is transported into the mitochondria, and an acetyl group derived from pyruvic acid combines with coenzyme-A present in the mitochondria to form acetylcoenzyme- A, which is transported back into the cytoplasm.

- 4. Choline, the precursor for Ach, is actively transported into the neuronal terminal from the synaptic cleft via Na^+ (sodium) and choline transporters.
- 5. Ach is synthesized in the cytoplasm of the nerve terminal from choline and acetylcoenzyme-A in the presence of an enzyme, **choline acetyltransferase**.
- 6. Ach is then transported into vesicles and stored there.
- 7. It is then released into the synaptic cleft by exocytosis and hydrolyzed by **acetylcholinesterase**.



- **Removal**
- **acetylcholinesterase** is present on the outer surfaces of the nerve terminal(prejunctional site) and the effector cell (postjunctional site).
- This enzyme hydrolyses Ach in the junctional extracellular space; **choline** liberated in this reaction re-enters the nerve terminal and is again used for the synthesis of Ach.

Distribution – two constelations

- 1. The **basal forebrain constellation** **is located in the telencephalon,** medial and ventral to the basal ganglia.
- The **basal nucleus of Meynert** provides cholinergic innervation to the entire neocortex, amygdala, hippocampus, and thalamus.
- **The medial septal nuclei** provide cholinergic innervation to the cerebral cortex, hippocampus, and amygdala.

- 2. The second constellation includes cholinergic neurons located in the **dorsolateral tegmentum of the pons** **that** project to the basal ganglia, thalamus, hypothalamus, medullary reticular formation, and deep cerebellar nuclei.
- 3. Ach is a neurotransmitter of neuromuscular synapse, preganglionic sympathetic and preganglionic and posganglionic parasympathetic neurons

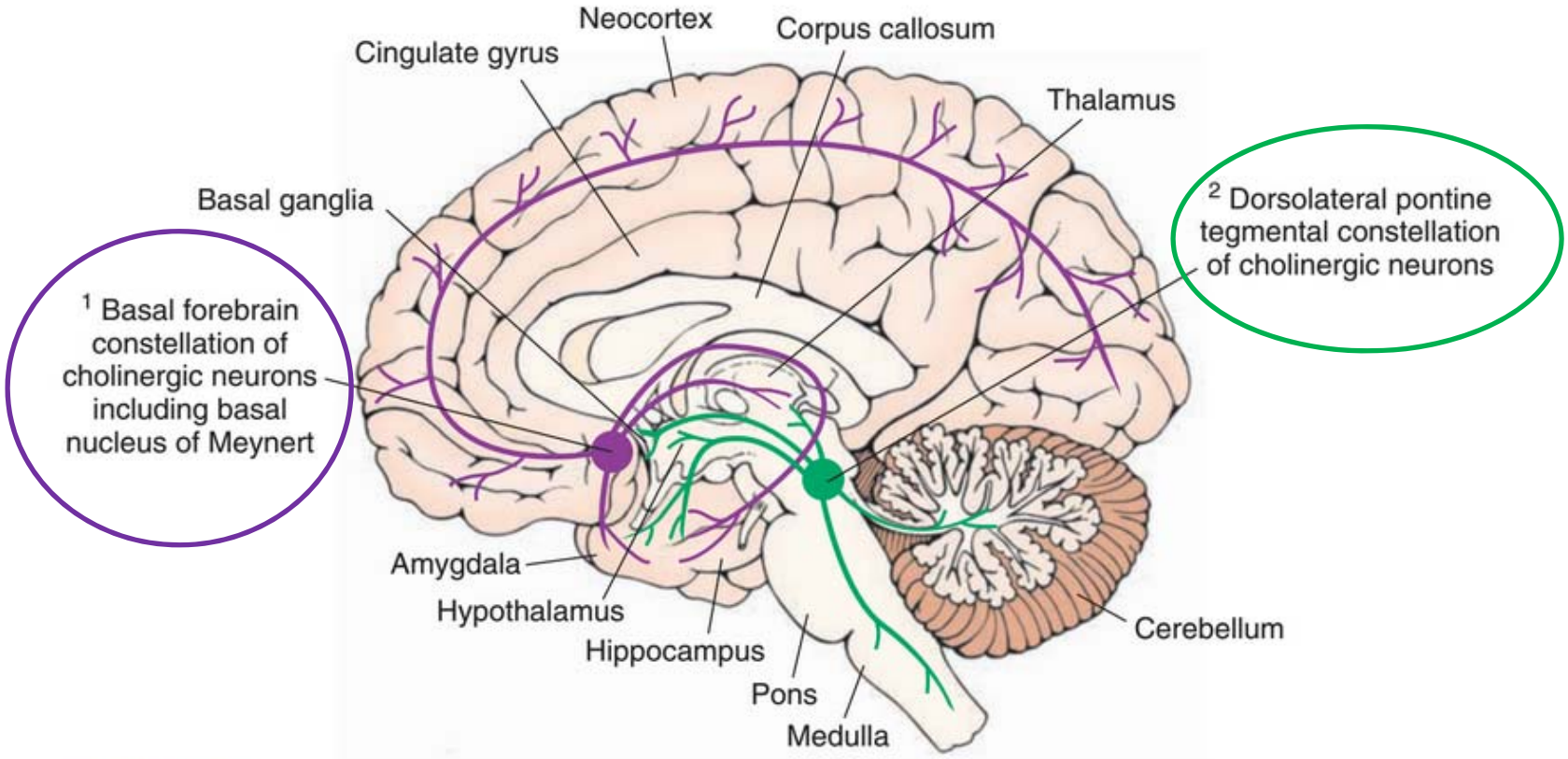
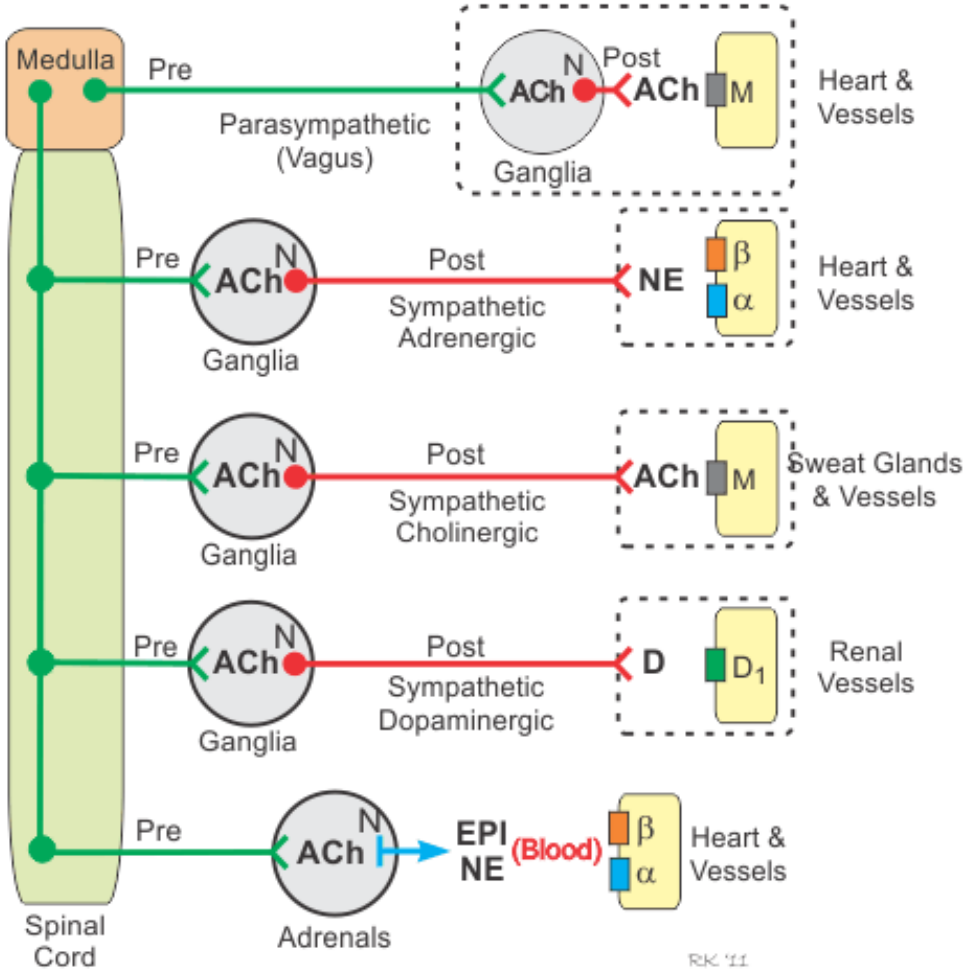


FIGURE 7.6 Major cholinergic cell groups. Note two major constellations of cholinergic neurons: cholinergic neurons located in the basal forebrain constellation, including the basal nucleus of Meynert, and cholinergic neurons located in the dorsolateral tegmentum of the pons.



CNS = central nervous system; Pre = preganglionic; Post = postganglionic;
ACh = acetylcholine; N = nicotinic receptor; NE = norepinephrine; EPI = epinephrine;
D = dopamine; M = muscarinic receptor; β = β-adrenoceptor; α = α-adrenoceptor;
D_1 = dopaminergic receptor

Ach is a neurotransmitter of:

a) neuromuscular synapse,

b) preganglionic sympathetic,

c) preganglionic and postganglionic parasympathetic neurons

Ach receptors

- **Ionotropic** nicotinic (neuronal and muscular nAChR)
- Neuronal nAChR is similar to muscle nAChR except that it is a complex of five subunits of two proteins (alpha and beta).

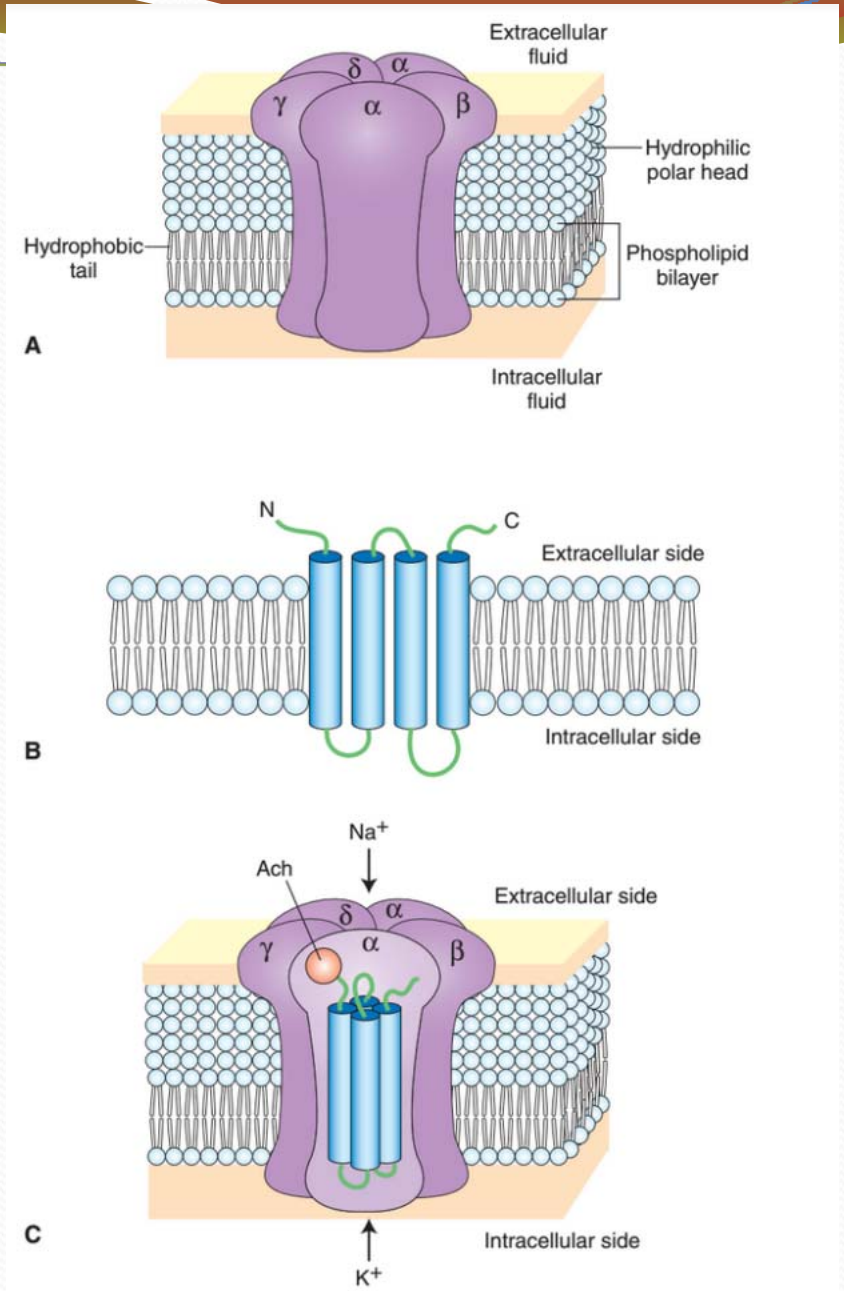


FIGURE 7.17 Nicotinic acetylcholine receptor (nAChR). **(A)** Fetal nAChR at the neuromuscular junction consists of five subunits of four proteins (alpha, beta, gamma, and delta). In adult nAChR, γ-subunit is substituted by an ϵ-subunit. **(B)** Each subunit spans the membrane four times. *N* and *C* represent amino (NH_2) and carboxyl (COOH) terminals, respectively. **(C)** The transmembrane domains from five subunits surround a central pore of the channel. Acetylcholine (Ach) binds to the α-subunit and opens the channel to allow influx of Na^+ (sodium) and efflux of K^+ (potassium).

Ach receptors

- **Metabotropic** muscarinic (M1-M5)
- M1 an M3 work through IP_3/DAG system and inactivate K^+ channels
- M2, M4 and M5 inhibit adenilil cyclase (decrease intracellular concentration of cAMP) and activate K^+ channels.

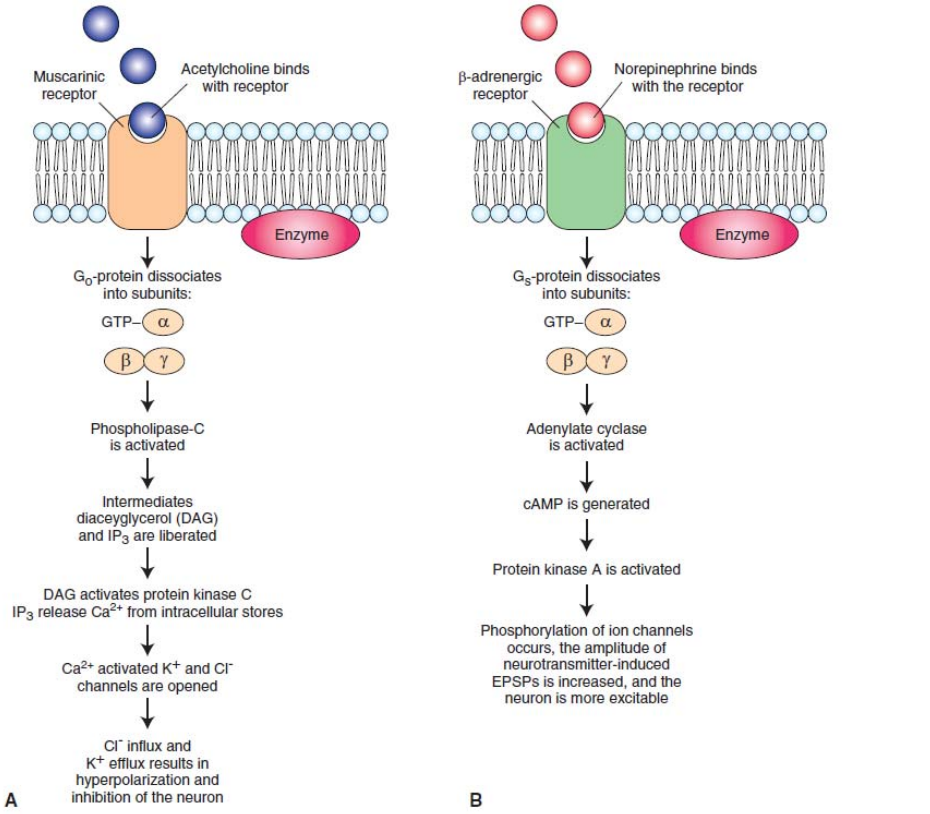


FIGURE 8–21 Mechanisms by which metabotropic receptors mediate responses to different transmitters. (A) Events that follow binding of acetylcholine to a muscarinic receptor. (B) Events that follow binding of norepinephrine to a β-adrenergic receptor. GTP = guanosine triphosphate; cAMP = cyclic adenosine monophosphate; EPSPs = excitatory postsynaptic potentials; Ca^{2+} = calcium; K^+ = potassium; Cl^- = chloride.

- AGONIST of nicotinic acetylcholine receptor - **NICOTINE**
- ANTAGONIST of nicotinic rec: **curare, α-bungarotoxin**
- AGONIST of muscarinic receptors: **muscarine**
- ANTAGONIST of muscarinic receptors: **atropine, scopolamine**
- ireverzibile inhibitors: **nerve toxins**
- reverzibile inhibitors: **neostigmin, fizostigmin**

- **Physiological and Clinical Considerations**
- regulation of forebrain activity during cycles of sleep and wakefulness
- Cholinergic neurons of the basal forebrain constellation are involved in learning and memory and have been implicated in **Alzheimer's disease.**
- There is a dramatic loss of cholinergic neurons in the basal nucleus of Meynert and Ach in the cortex of these patients.
- treatment with donepezil (Aricept), an acetylcholinesterase inhibitor, is indicated for mild to moderate dementia in patients with Alzheimer's disease.

Monoamine neurotransmitters

- **Catecholamines**: dopamine,norepinephrine, epinephrine; synthetised from *tyrosine*
- **Indoleamines**: serotonin (from triptofan) and histamine (from histidin)
- Monoamines are located in small and medium vesicles with dense core.

Catecholamines:
dopamine
norepinephrine
epinephrine
synthetised from *tyrosine*

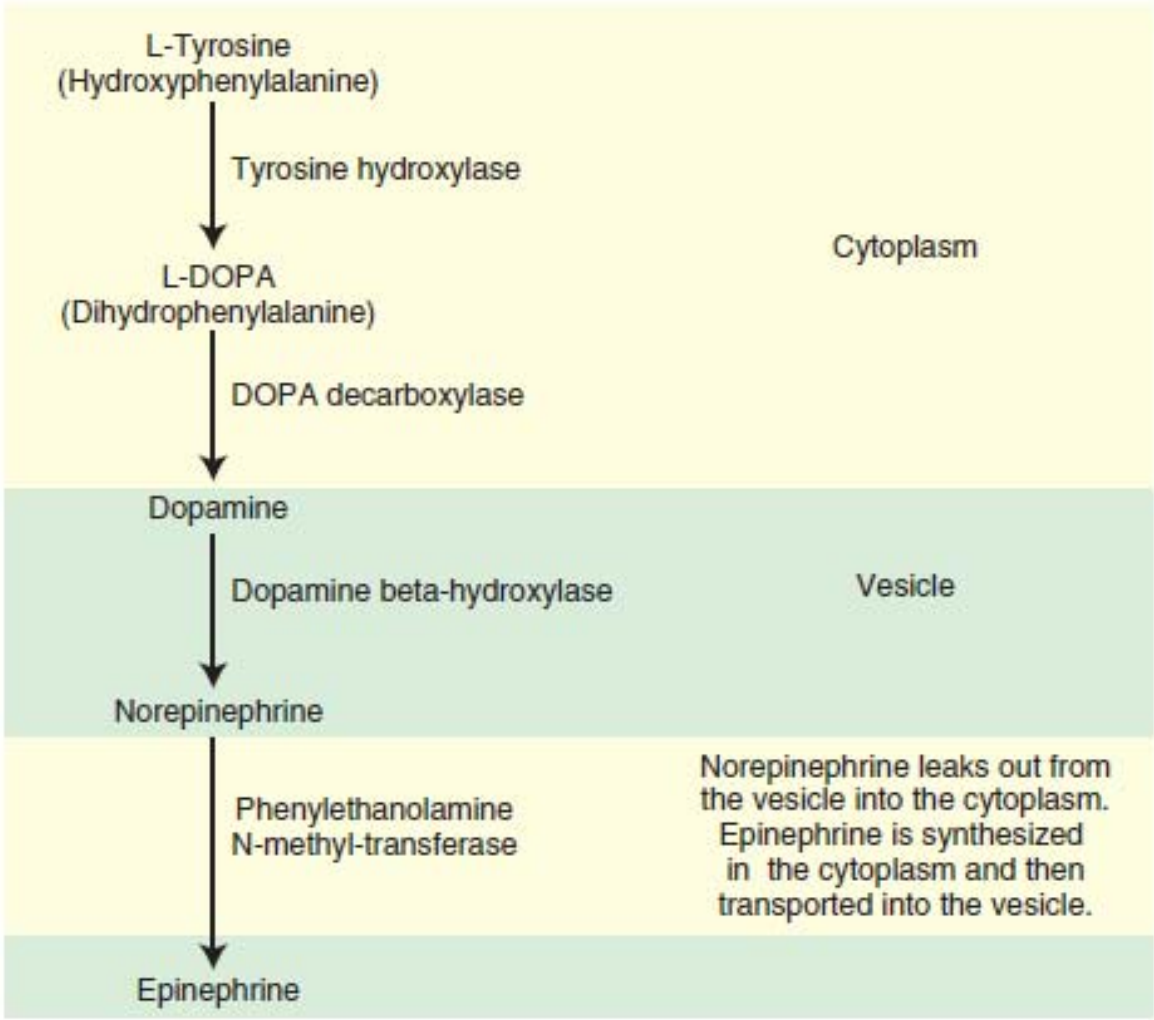


FIGURE 8–9 Steps involved in the synthesis of catecholamines.

Dopamine: Synthesis and Removal

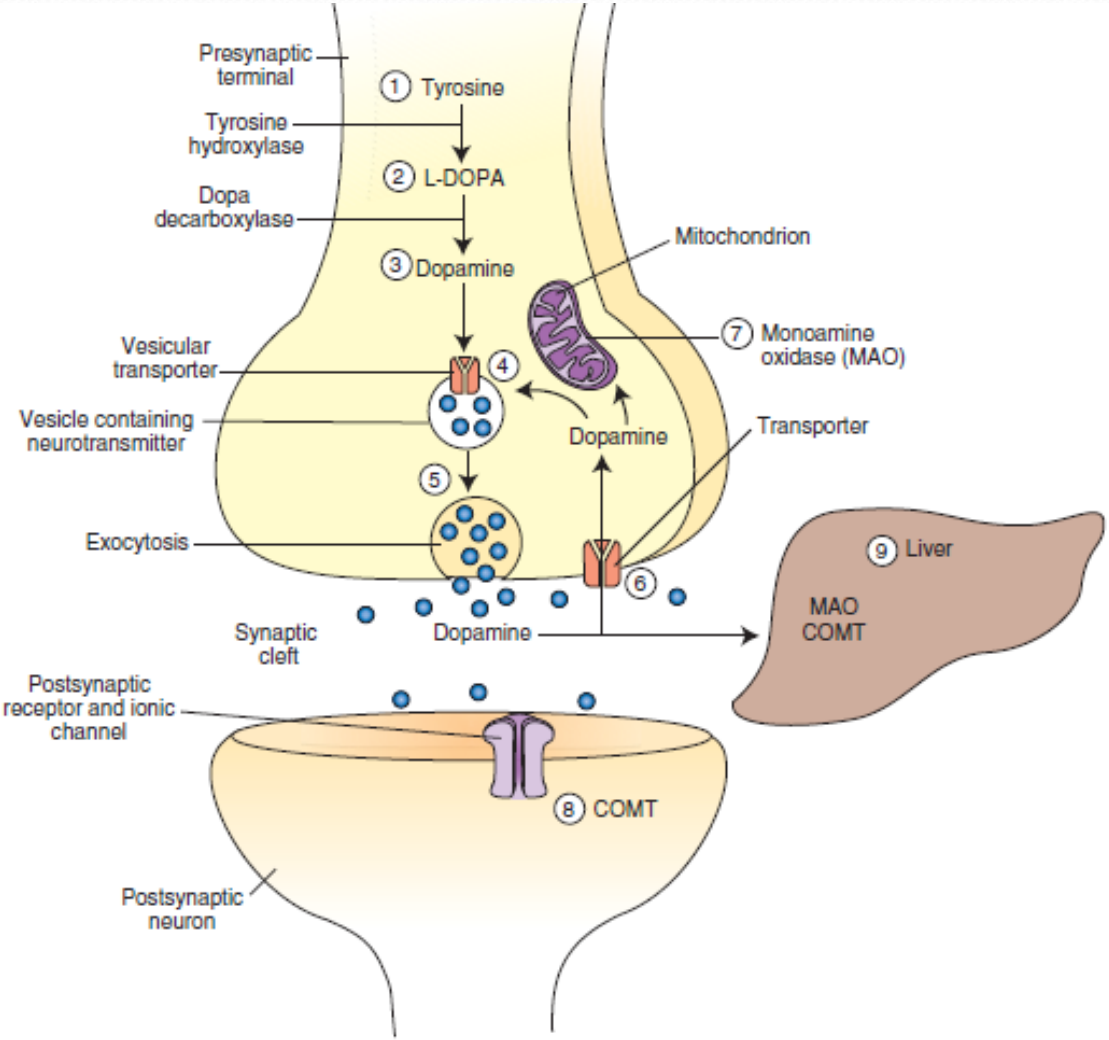
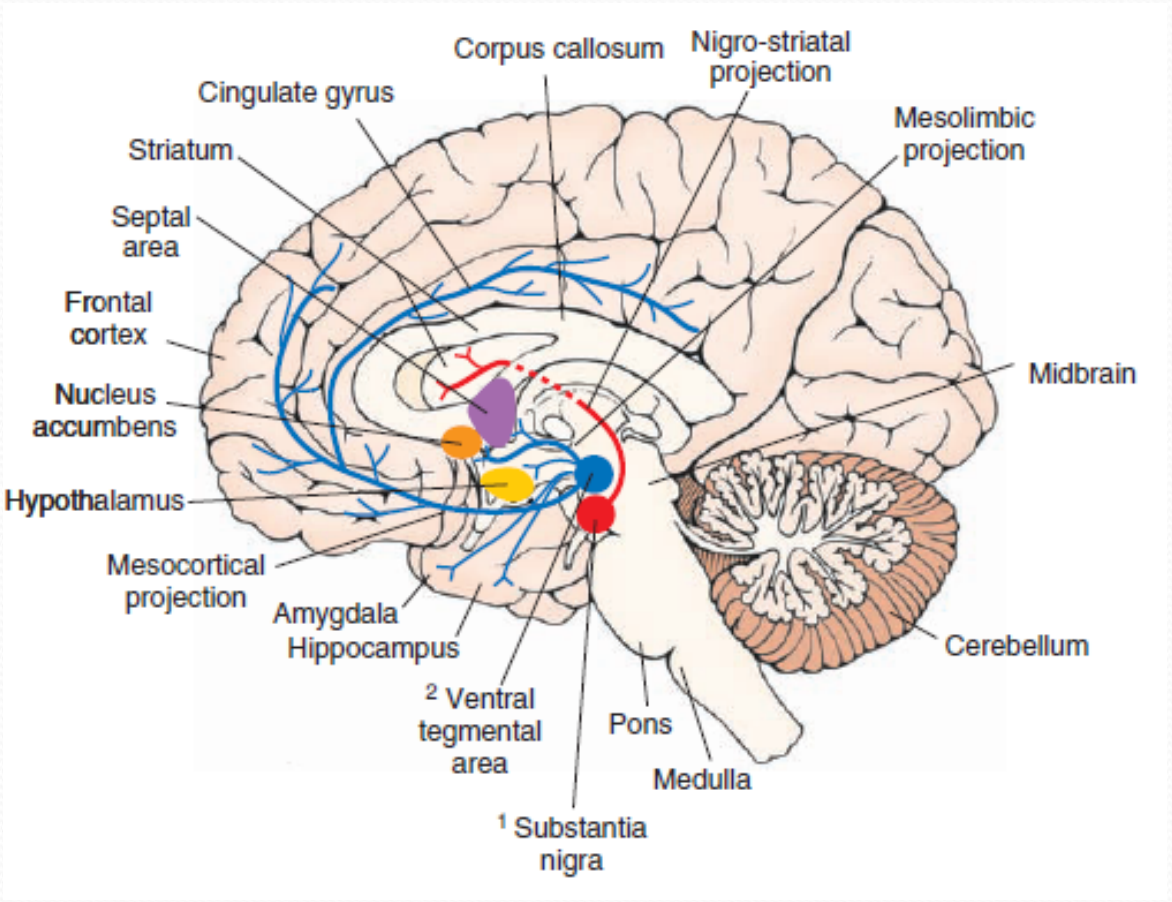


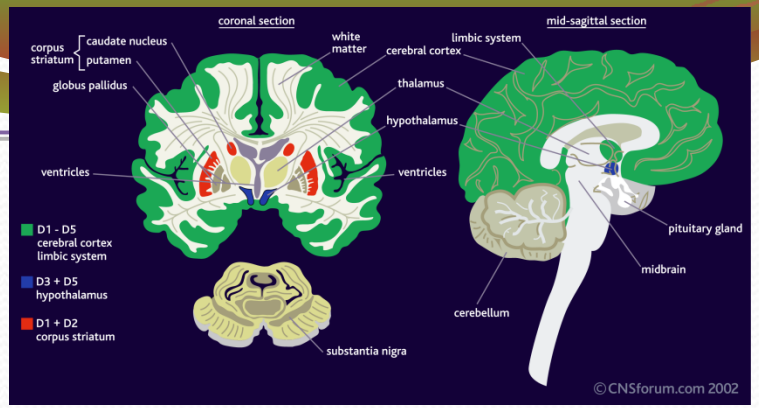
FIGURE 8–10 Steps involved in the synthesis and release of dopamine. COMT = catechol-O-methyltransferase.

Dopamine: Distribution

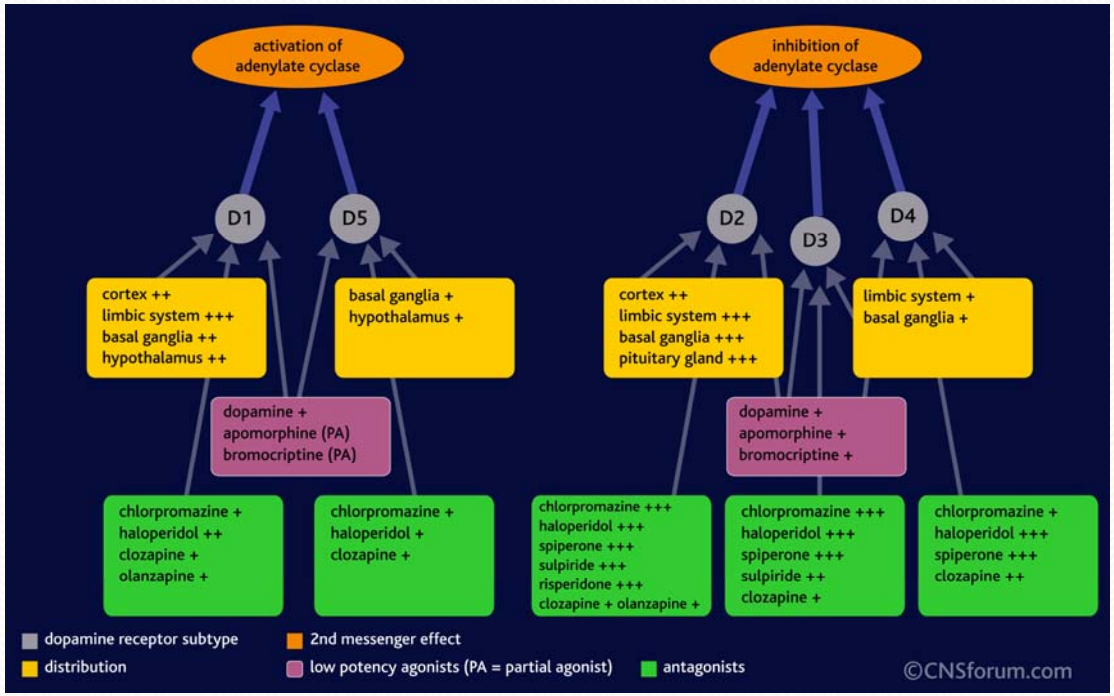
- **Substantia nigra**
- **Ventral tegmental area**
- The **hypothalamic arcuate nucleus**



Dopamine Receptors

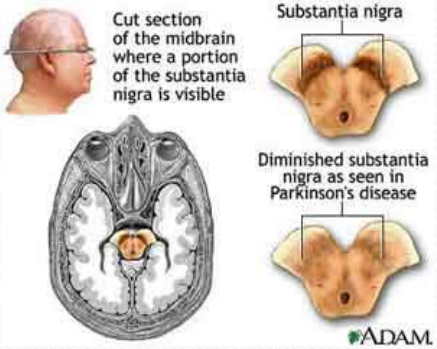


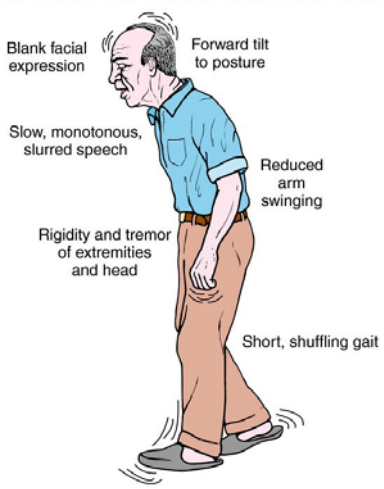
- metabotropic
- D1, D5 activate adenilil cyclase – role in Parkinson's disease;
- D2, D3, D4 inhibit it – role in schizophrenia
- D1 important in nigrostriatal projections

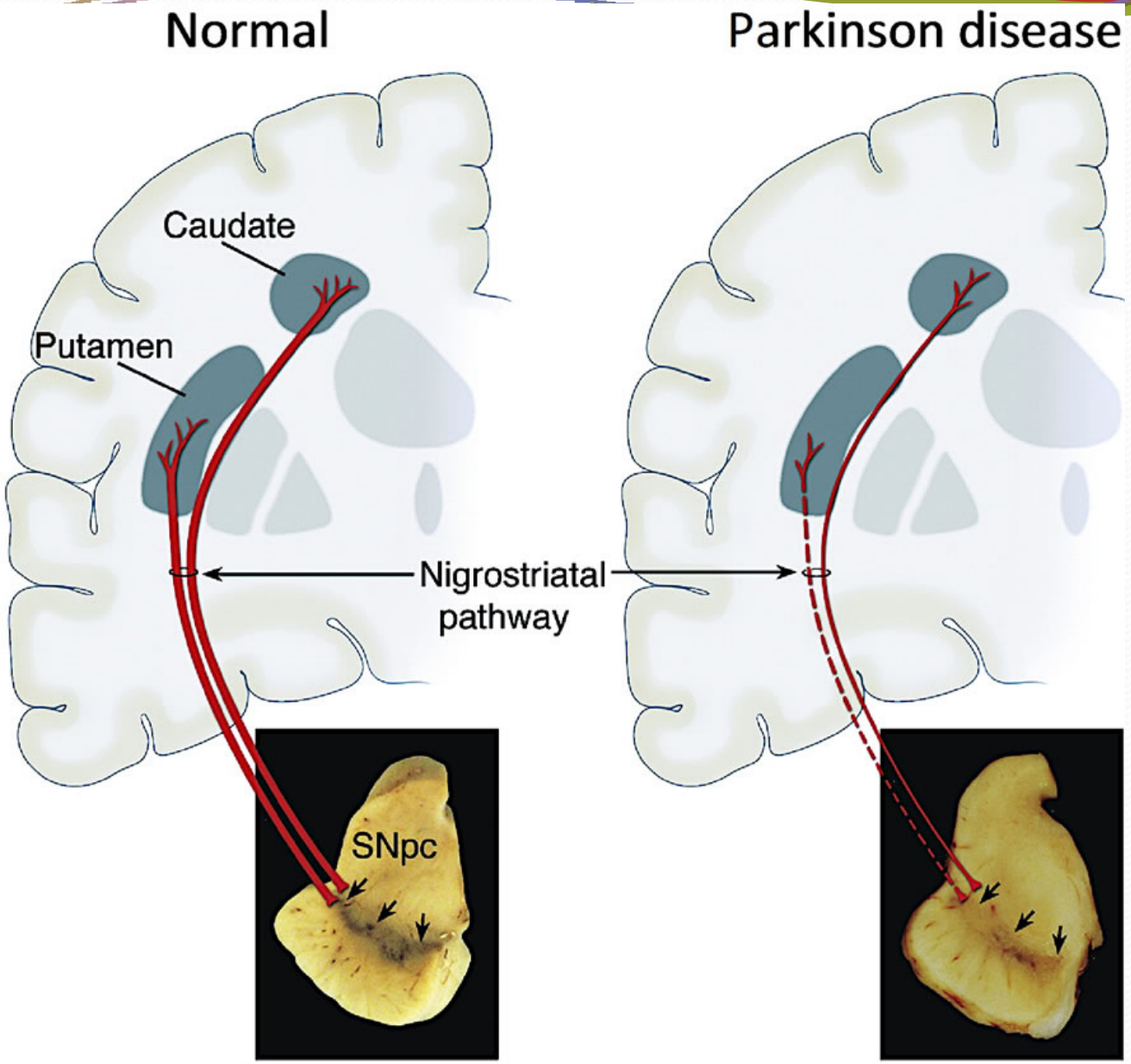


Physiological and Clinical Considerations

- ***Parkinson's Disease***
- "mask-like face"
- slowness of movement
- rigidity of the extremities and the neck
- tremors in the hands
- Dopaminergic neurons located in the substantia nigra are degenerated
- drug therapy: to replace the deficiency of the dopamine in the basal ganglia
- dopamine does not cross the blood-brain barrier - (L-DOPA (levodopa) is administered)






Normal
Parkinson disease
Caudate
Putamen
Nigrostriatal
pathway
SNpc

- ***Psychotic Disorders***
- schizophrenia
- increased activity at dopaminergic synapses
- ***Cocaine Drug Abuse***
- blocks the reuptake of dopamine
- Elevated levels of dopamine in certain brain circuits may be responsible for the euphoric effects of cocaine
- Dopaminergic projections from the VTA to the limbic structures (nucleus accumbens), may be involved in emotional reinforcement and motivation.

Norepinephrine: Synthesis and Removal

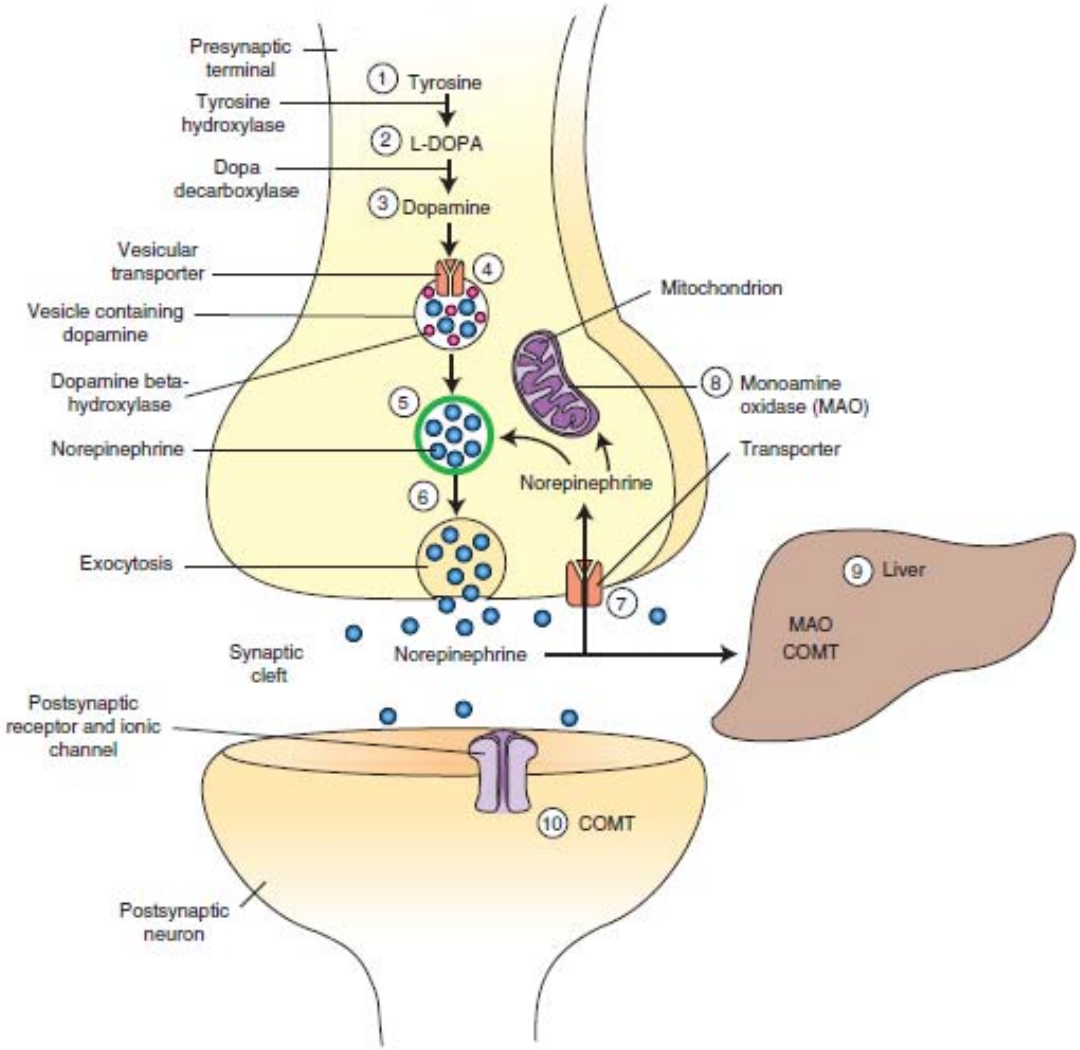
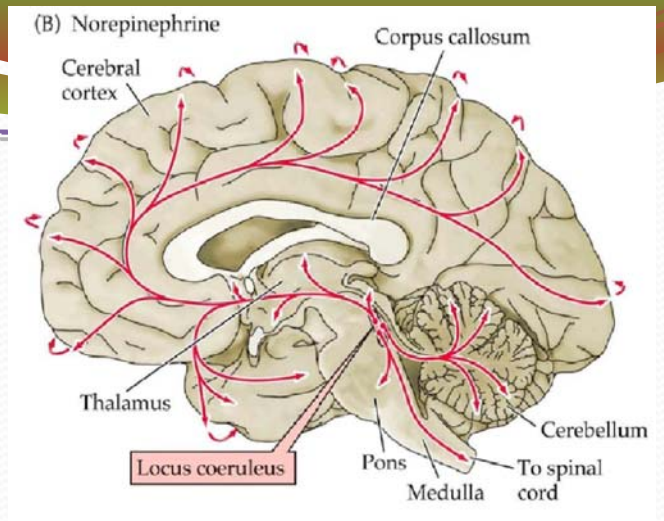


FIGURE 8–12 Steps involved in the synthesis and release of norepinephrine. COMT = catechol-O-methyltransferase.

- **Autoinhibition and Negative Feedback**
- Activation of presynaptic adrenergic receptors results in inhibition of the release of norepinephrine. This process is known as **autoinhibition**
- It is distinct from negative feedback in which synthesis of the transmitter (norepinephrine in this case) is blocked at its rate- limiting step (i.e., conversion of tyrosine to DOPA by tyrosine hydroxylase).

Distribution



- **locus ceruleus (also known as "A6** group of neurons") that is located in the pons
- projections through the central tegmental tract and the medial forebrain bundle to the thalamus, hypothalamus, limbic forebrain structures (cingulate and parahippocampal gyri, hippocampal formation, and amygdaloid complex), and the cerebral cortex
- **Role in** sleep and wakefulness, attention, and feeding behaviors

- **Physiological and Clinical Considerations**
- neurotransmitter of postganglionic sympathetic nerve terminals.
- psychiatric disorders such as depression.
- tricyclic antidepressants (desimipramine) inhibit the reuptake of norepinephrine at the nerve terminals

Norepinephrine receptors

- Norepinephrine receptors α1, α2, β1, β2, β3
- all metabotropic
- α 1 – through PLC on IP3/DAG system
- α 2 - inhibits adenylyl cyclase and lowers concentration of cAMP
- β 1 and β2 activate adenylyl cyclase and increase concentration of cAMP

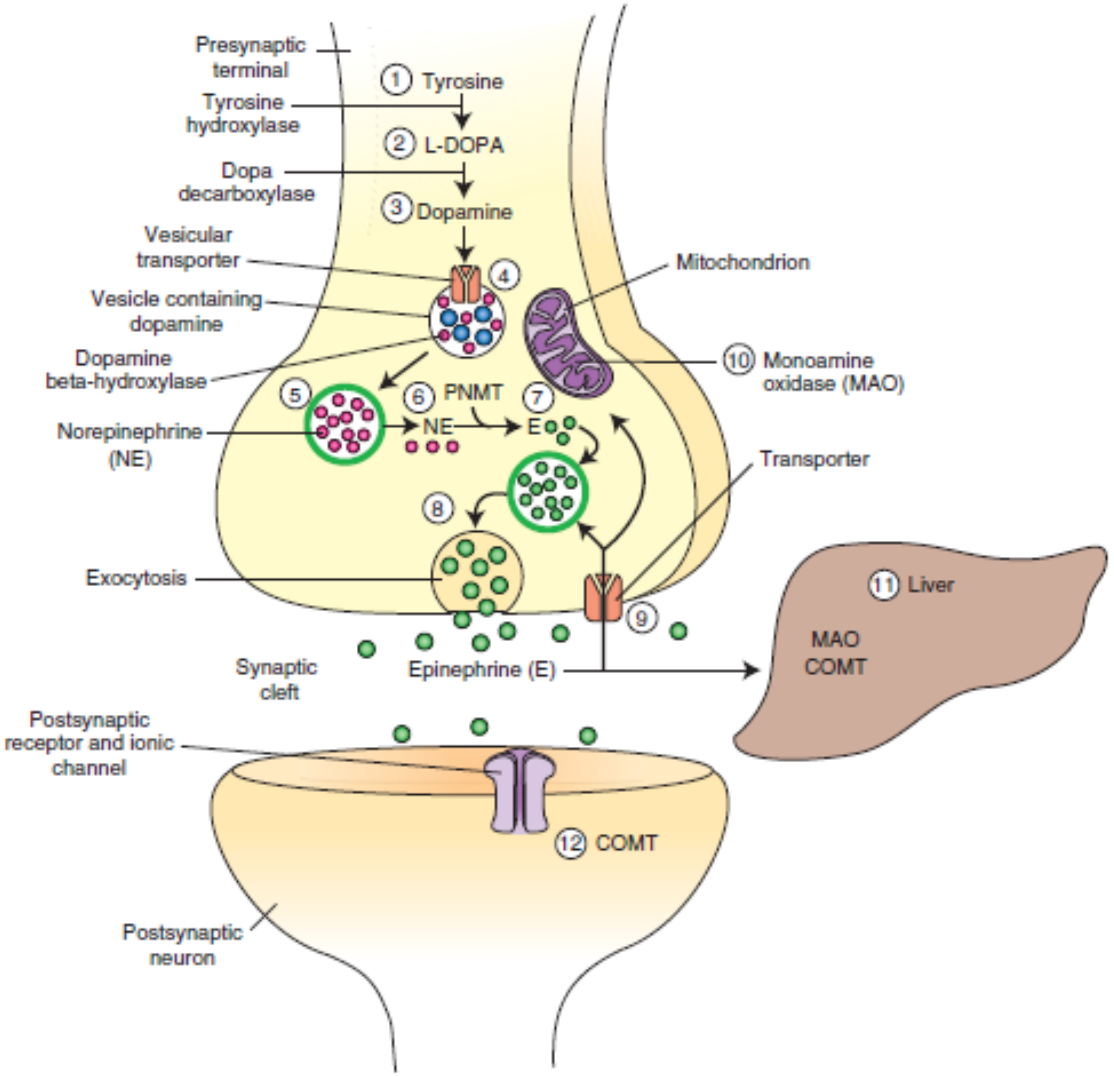


FIGURE 8–13 Steps involved in the sy
release of epinephrine. COMT =
methyltransferase; PNMT = phenyleth
N-methyl-transferase.

Indoleamines: *Serotonin*

- **Synthesis and Removal**
- does not cross the blood-brain barrier
- brain cells must synthesize their own serotonin
- Tryptophan serves as a substrate for serotonin synthesis

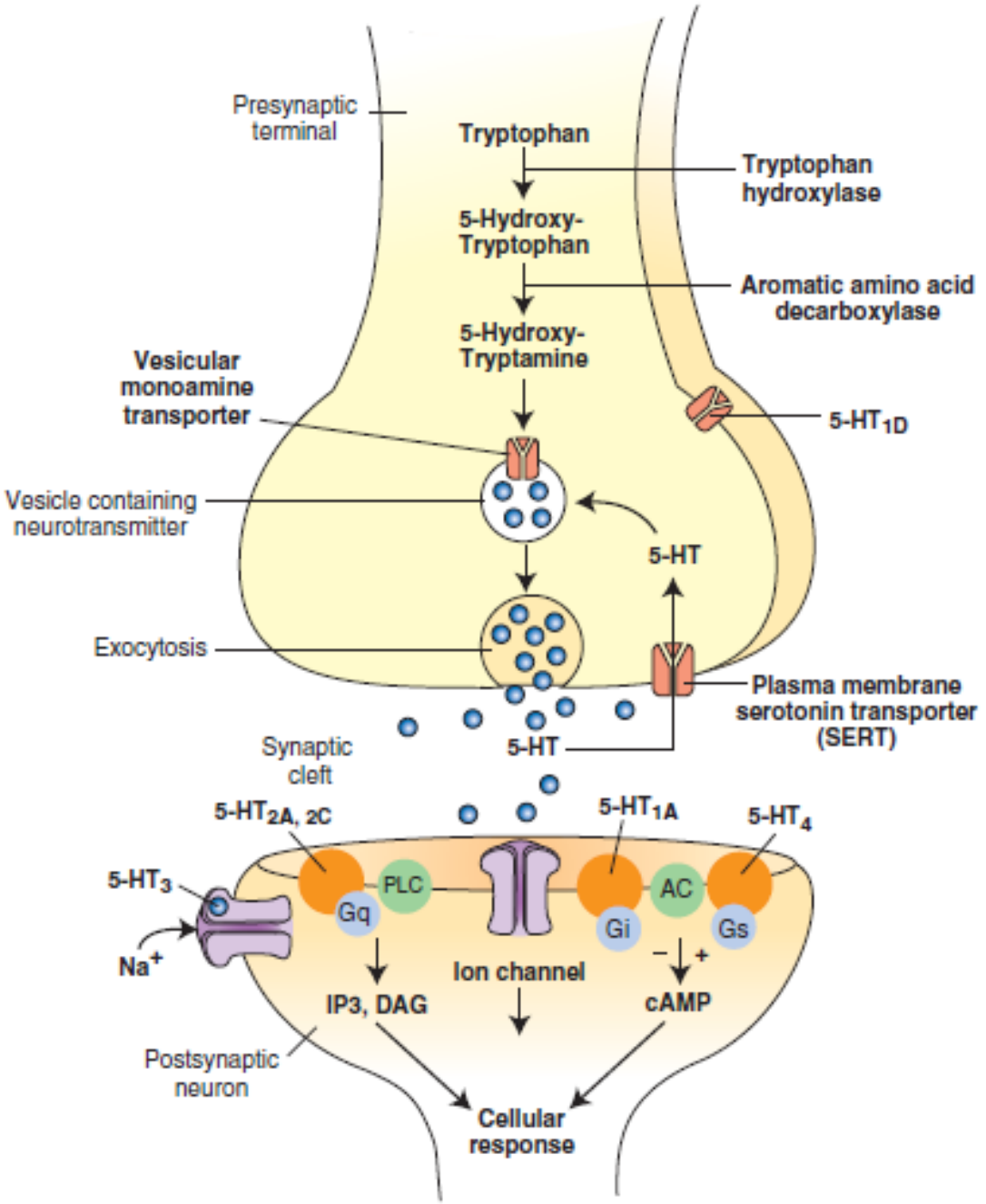


FIGURE 8–14 Steps involved in the synthesis and release of serotonin. The distribution of some 5-HT receptors on different components of the serotonergic synapse is also shown. AC = adenylyl cyclase; cAMP = cyclic adenosine monophosphate; DAG = diacylglycerol; Gi, Go, Gq = different G-proteins; IP3 = inositol triphosphate; 5-HT_{1A}, 5-HT_{1D}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, 5-HT_4 = different 5-HT receptors.

- **Distribution**
- midline **raphe nuclei of the medulla, pons**, and upper brainstem
- Central nervous system- 1% of all serotonin
- Enterocromaphine cells of intestines contain about 90% of all serotonin
- Trombocytes – 2% of all serotonin

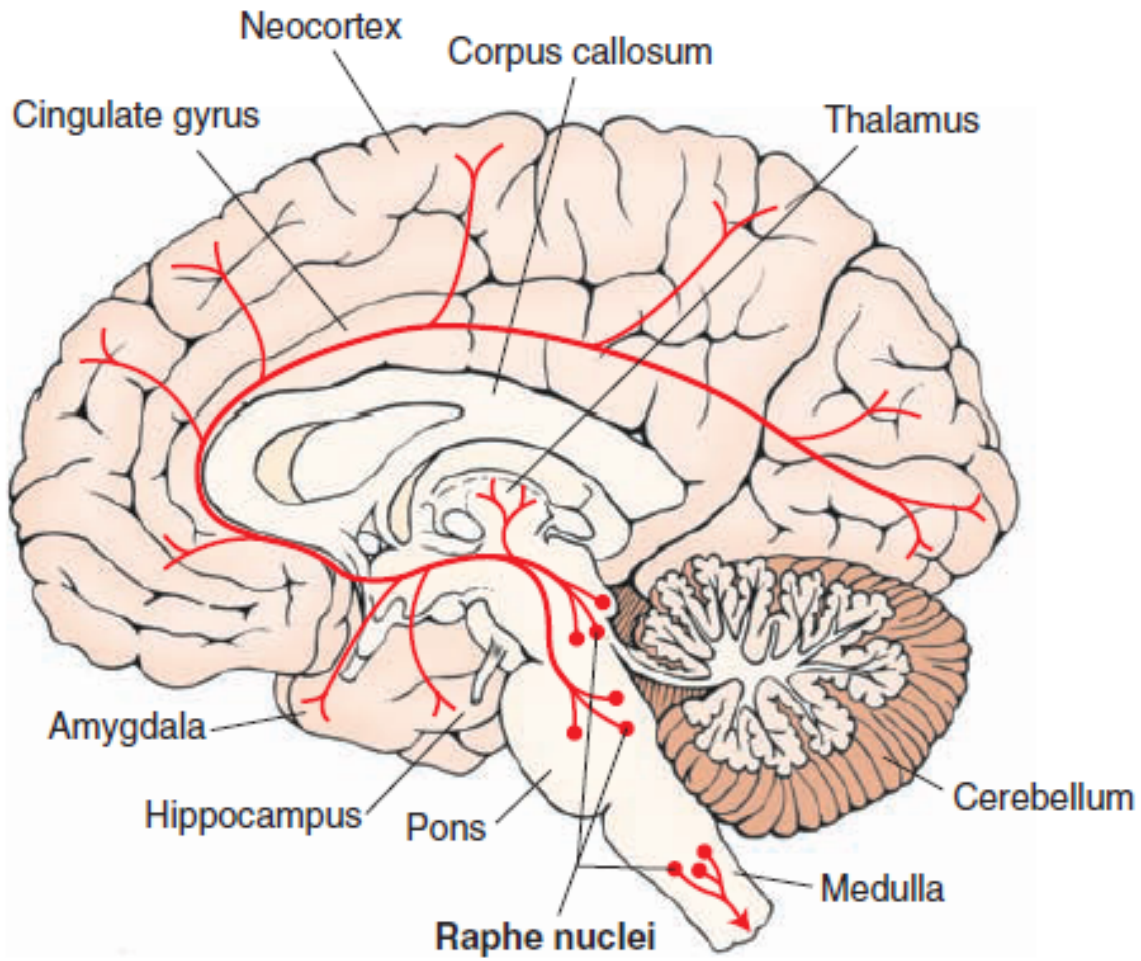
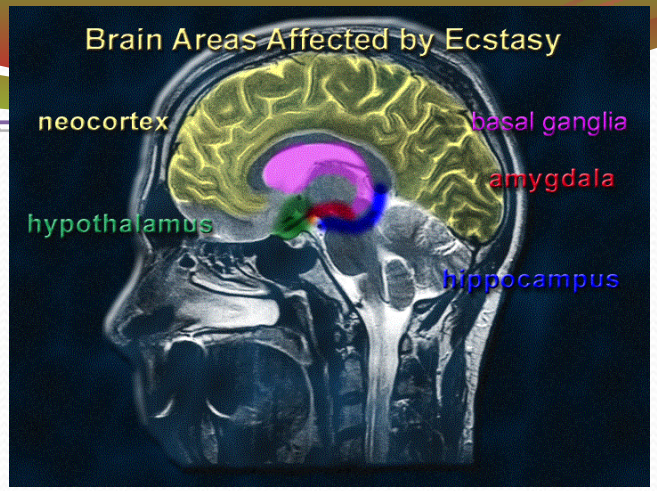


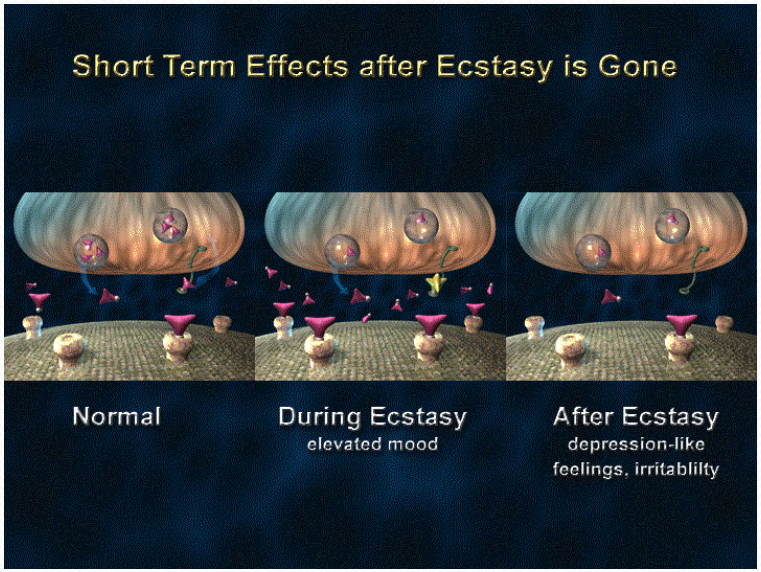
FIGURE 8–15 Major serotonin-containing neurons and their projections.

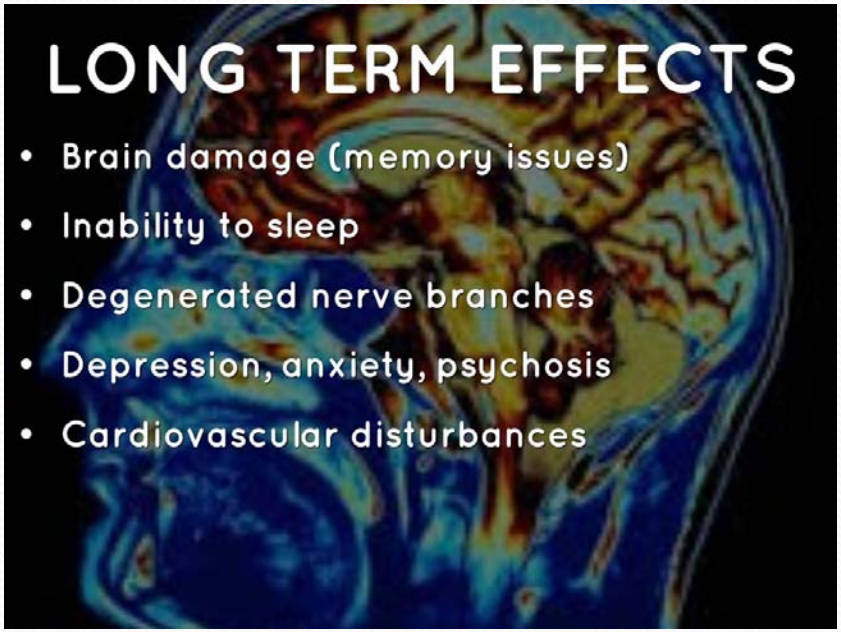
- **Physiological and Clinical Considerations**
- dorsal horn regulate the release of enkephalins, which inhibit pain sensation
- mediate affective processes, such as aggressive behavior and arousal
- in the **pineal gland** is a precursor for the synthesis of **melatonin, which is a neurohormone** involved in regulating sleep patterns.

- plays an important role in depression.
- **serotonin- specific reuptake inhibitors (SSRIs) are used** in the treatment of depression, anxiety disorders, and some personality disorders - **fluoxetine (Prozac)**
- **Sumatriptan (Imitrex) is a** 5-HT_{1D} receptor agonist. It is a vasoconstrictor of intracranial arteries and has proved useful in treating migraine headaches.

- **“Designer Drugs” of Abuse and Their Relationship With Serotonin.**
- **Ecstasy** has been used as a recreational drug by young adults (“rave parties”)







Serotonin receptors

- $5HT_1$, $5HT_2$ and $5HT_3$
- $5HT_3$ are the only ionotropic
- $5HT_2$ works through phospholipasis C na IP3/DAG system
- $5HT_1$ inhibits adenylyl cyclase and lowers concentration of cAMP
- Serotonin receptors 5-HT_1, 5-HT_2, 5-HT_3
  - Autoreceptors 5-HT_{1A} receptors on soma and dendrites of serotonergic neurons.

5-HT receptors

Receptor *	***Distribution***	***Effector mechanism***
5-HT_{1A}	Hippocampus, amygdala, septum, entorhinal cortex, hypothalamus, raphe nuclei	Inhibition of adenylyl cyclase, opening of K^+ channels
5-HT_{1B}		Inhibition of adenylyl cyclase
5-HT_{1Da}	Not distinguishable from 5-HT_{1Db}	Inhibition of adenylyl cyclase
5-HT_{1Db}	Substantia nigra, basal ganglia, superior colliculus	Inhibition of adenylyl cyclase
5-ht_{1E}	?	Inhibition of adenylyl cyclase
5-ht_{1F}	Cerebral cortex, striatum, hippocampus, olfactory bulb	Inhibition of adenylyl cyclase
5-HT_{2A}	Claustrum, cerebral cortex, olfactory tubercle, striatum, nucleus accumbens	Stimulation of phosphoinositide-specific phospholipase C (IP3/DAG), closing of K+ channels
5-HT_{2B}	?	Stimulation of phosphoinositide-specific phospholipase C (IP3/DAG)
5-HT_{2C}	Choroid plexus, globus pallidus, cerebral cortex, hypothalamus, septum, substantia nigra, spinal cord	Stimulation of phosphoinositide-specific phospholipase C (IP3/DAG)

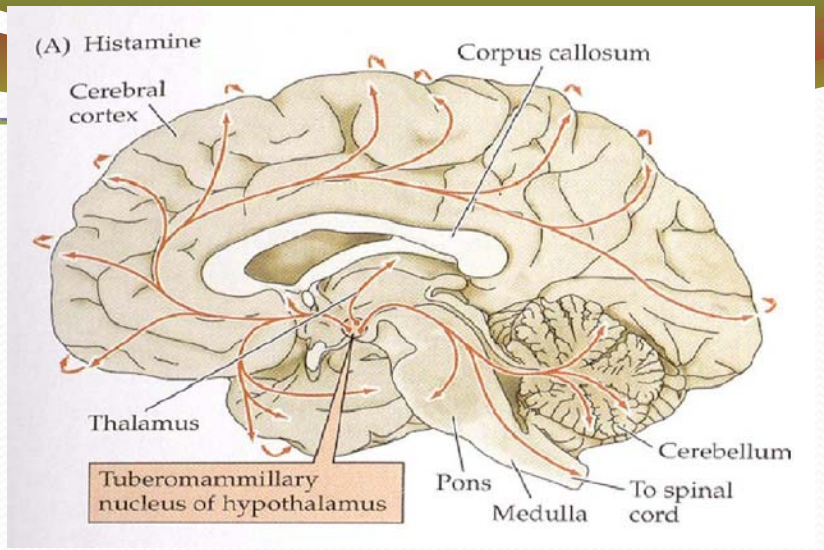
5-HT receptors

Receptor	***Distribution***	***Effector mechanism***
$5\text{-}HT_3$	Hippocampus, entorhinal cortex, amygdala, nucleus accumbens, solitary tract nerve, trigeminal nerve, motor nucleus of the dorsal vagal nerve, area postrema, spinal cord	Ligand-gated cation channel
$5\text{-}HT_4$	Hippocampus, striatum, olfactory tubercle, substantia nigra	Stimulation of adenylyl cyclase
$5\text{-}ht_{5A}$	?	Inhibition of adenylyl cyclase
$5\text{-}HT_{5B}$	?	?
$5\text{-}ht_6$	?	Stimulation of adenylyl cyclase
$5\text{-}HT_7$	Cerebral cortex, septum, thalamus, hypothalamus, amygdala, superior colliculus	Stimulation of adenylyl cyclase
*Lower-case appellations are used in some cases because the functions mediated by these receptors in intact tissue are presently unknown.		

Imidazole amines: *Histamine*

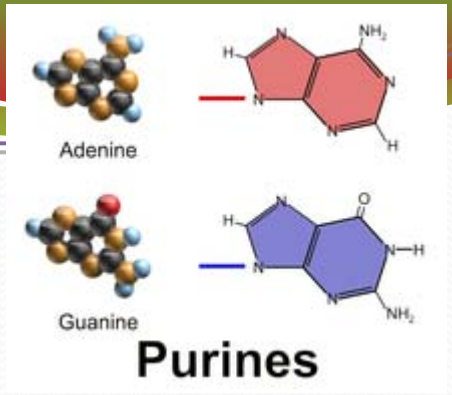
- **Synthesis and Removal**
- In the periphery, **histamine is synthesized** in mast cells.
- does not cross the blood-brain barrier
- Brain cells synthesize their own histamine from histidine, which enters the brain by active transport.
- Histamine is metabolized by two enzymes—histamine methyltransferase and diamine oxidase (histaminase)

Histamine



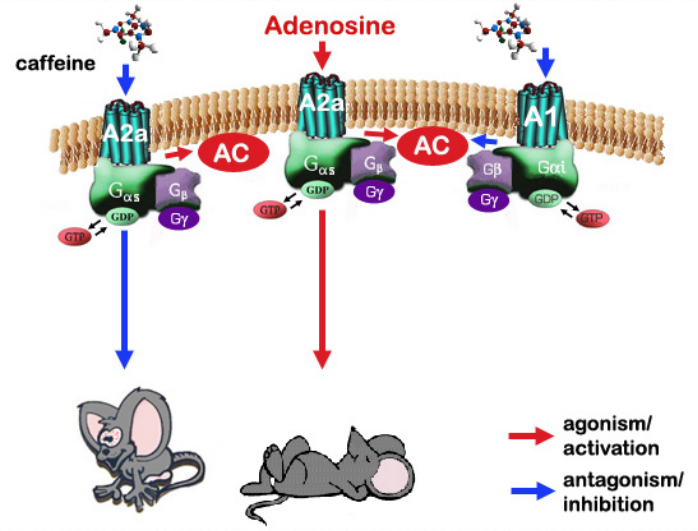
- **Distribution:**
- Hypothalamus – premammilary region

- **Physiological and Clinical Considerations**
- food and water intake
- thermoregulation and autonomic functions



Purines

- ATP (adenosine triphosphate) has been implicated as a neurotransmitter
- it is not stored in presynaptic vesicles and
- is not released in a Ca^{2+} dependent manner.
- Adenosine receptors: A1-A3
- Research



NEUROACTIVE PEPTIDES: Opioid Peptides

- β-endorphin
- Enkephalins
- Dynorphin

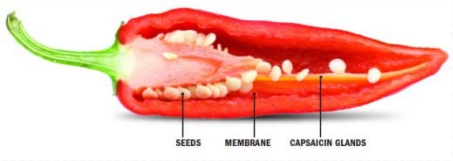
- **Physiological and Clinical Considerations**
- Intracerebroventricular injection of opioid peptides (e.g., β- endorphin) produces analgesia.
- no side-effects like addiction
- modulation of pain sensation
- regulating blood pressure, temperature, feeding, aggression, and sexual behavior.

Tachykinins: Substance P

- **Location**: The dorsal root ganglia projecting to the substantia gelatinosa of the spinal cord
- **Role:** **nociceptors** because they transmit information regarding tissue damage to the pain processing areas located in the CNS.
- Substance P has been implicated as one of the neurotransmitters in mediating pain sensation

- a topical cream containing **capsaicin** has been used as an analgesic in the treatment of viral neuropathies, arthritic conditions

- **Capsaicin**, the pungent substance present in hot chili peppers, mediates its actions via vanilloid receptors, which are present exclusively on the membranes of primary afferent neurons



- With repeated applications, the vanilloid receptors may become desensitized, thus reducing pain sensations

- With prolonged use, capsaicin causes death of primary afferent neurons as a consequence of increased intracellular Ca2+ concentrations.

GASEOUS NEUROTRANSMITTERS

- **Nitric oxide(NO)**
  - Differences from other transmitters
- **carbon monoxide (CO)**
- **Physiological and Clinical Considerations**


Thank you and
Study Neuroscience!